Serum lactate dehydrogenase and C reactive protein levels in sepsis and its correlation with APACHE-II score

Submitted in partial fulfilment of Requirements for

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CERTIFICATE

This is to certify that this dissertation entitled **"Serum lactate dehydrogenase and C reactive protein levels in sepsis and its correlation with APACHE-II score**" submitted by **Dr. M.ANAND** appearing for M.D. Branch I - General Medicine Degree examination in March 2012 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfilment of regulations of the TamilNadu Dr. M.G.R. Medical University, Chennai. I forward this to the TamilNadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I solemnly declare that the dissertation titled **"Serum lactate dehydrogenase and C reactive protein levels in sepsis and its correlation with APACHE-II score"** is done by me at Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai during 2010-2011 under the guidance and supervision of **Prof.Dr.A.RADHAKRISHNAN., M.D.** The dissertation is submitted to The Tamilnadu Dr.M.G.R. Medical University towards the partial fulfilment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

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ABBREVIATIONS

APACHE - Acute Physiology and Chronic Health Evaluation

ARDS - Acute respiratory distress syndrome

COPD - Chronic Obstructive Pulmonary Disease

CRP - C-reactive protein

DIC - Disseminated Intravascular Coagulation

DM - Diabetes mellitus

ESR - Erythrocyte Sedimentation Rate

IL-1 - Interleukin 1

IL-6 - Interleukin 6

LDH - Lactate Dehydrogenase

MODS - Multiple-organ dysfunction syndrome

PCT - Procalcitonin

SAPS - Simplified Acute Physiology Score

SIRS - Systemic inflammatory response syndrome

SOFA - Sequential Organ Failure Assessment

TNF alpha - Tumor necrosis factor alpha

CONTENTS

INTRODUCTION

INTRODUCTION:

The word **sepsis** originated from the old Greek word meaning "**putrefaction**". Nowadays, this term is used to describe the host systemic response to infectious stimuli that is characterised by clinical, haemodynamic, biochemical and inflammatory responses[1] . Sepsis is still one of the leading causes of death in the critically ill patients[2].

In daily practice, clinicians are often faced with two dilemmas: 1.whether a patient is infected or not, and 2.whether the antibiotic therapy being given is effective. The distinction between infection and sepsis is frequently difficult to make. Infection without sepsis can occur if the process remains localised. A sepsis-like syndrome without infection is also a frequent finding in conditions such as trauma and pancreatitis[3].

The attention of the clinician must be directed towards the early diagnosis of infection[4] . However, bacteriological confirmation may be difficult to obtain and negative cultures do not exclude the presence of infection. In addition, manifestations of sepsis such as fever, leukocytosis and tachycardia are neither specific nor sensitive for infection, nor for monitoring the response to therapy[5] .

Increasing understanding of the various inflammatory cascade mechanisms has given new insights and provided several markers that, in conjunction with other manifestations of sepsis, can be useful as indicators of infection. **C-reactive protein (CRP)** is one such marker.

A marker of sepsis has been defined as "***a measure that identifies a normal biologic state or that predicts the presence or severity of a pathologic process or disease***."[7]

CRP levels are widely used as a relatively non-specific marker of inflammation. Many studies have demonstrated increased CRP levels in patients with sepsis; increasing or persistently high levels suggest a poor prognosis, while declining values are associated with a more favourable prognosis.

Elevated serum levels of the intracellular enzyme LDH in sepsis might result from various mechanisms including cellular injury related to bacterial toxins, ischemia and cytotoxic-reactive oxygen species generated during reperfusion. Various studies have confirmed the presence of elevated LDH levels in severe

sepsis. There is a study in US which predicted the development of ARDS in patients in sepsis based on serum LDH levels[8].

In the present study, **serum LDH and CRP concentrations in all patients admitted to the emergency ward with clinical sepsis were measured and compared their prognostic value in the assessment of severity and mortality.**

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES:

1. To analyse the **relationship of LDH and CRP** levels on admission to **APACHE-II** score in patients with sepsis.

2. To determine whether LDH and CRP levels can **predict morbidity and mortality** in patients with sepsis .

REVIEW OF LITERATURE

REVIEW OF LITERATURE:

Definitions

Animals mount both local and systemic responses to microbes that traverse their epithelial barriers and enter underlying tissues. Fever or hypothermia, leukocytosis or leukopenia, tachypnea, and tachycardia are the cardinal signs of the systemic response that is often called the ***systemic inflammatory response syndrome*** **(SIRS)**. SIRS may have an infectious or a non-infectious etiology. If infection is suspected or proven, a patient with SIRS is said to have ***sepsis*****.** When sepsis is associated with dysfunction of organs distant from the site of infection, the patient has ***severe sepsis***. Severe sepsis may be accompanied by hypotension or evidence of hypoperfusion. When hypotension cannot be corrected by infusing fluids, the diagnosis is ***septic shock***. These definitions were developed by consensus conference committees in 1992 and 2001 and have been widely used; there is evidence that the different stages may form a continuum.

Bacteremia - Presence of bacteria in blood, as evidenced by positive blood cultures

Septicemia - Presence of microbes or their toxins in blood

Systemic inflammatory response syndrome (SIRS)

Two or more of the following conditions:

1. fever (oral temperature >38°C) or hypothermia (<36°C);
2. tachypnea (>24 breaths/min);
3. tachycardia (heart rate >90 beats/min);
4. leukocytosis (>12,000/microL), leukopenia (<4,000/microL), or >10% bands; may have a non-infectious etiology

Sepsis - SIRS that has a proven or suspected microbial etiology

Severe sepsis (similar to "sepsis syndrome")

Sepsis with one or more signs of organ dysfunction—for example:

1. *Cardiovascular:* Arterial systolic blood pressure <90 mmHg or mean arterial pressure<70 mmHg that responds to administration of intravenous fluid
2. *Renal:* Urine output <0.5 mL/kg per hour for 1 hour despite adequate fluid resuscitation
3. *Respiratory:* Pa_{O2}/FI_{O2} <=250 or, if the lung is the only dysfunctional organ, <=200

4. *Hematologic:* Platelet count <80,000/microL or 50% decrease in platelet count from highest value recorded over previous 3 days
5. *Unexplained metabolic acidosis:* A pH <=7.30 or a base deficit >=5.0 mEq/L and a plasma lactate level >1.5 times upper limit of normal for reporting lab
6. *Adequate fluid resuscitation:* Pulmonary artery wedge pressure >=12 mmHg or central venous pressure >=8 mmHg

Septic shock

Sepsis with hypotension (arterial blood pressure <90 mmHg systolic, or 40 mmHg less than patient's normal blood pressure) for at least 1 hour despite adequate fluid resuscitation;

Or

Need for vasopressors to maintain systolic blood pressure >=90 mmHg *or* mean arterial pressure >=70 mmHg

Refractory septic shock

Septic shock that lasts for >1 hour and does not respond to fluid or pressor administration

Multiple-organ dysfunction syndrome (MODS)

Dysfunction of more than one organ, requiring intervention to maintain homeostasis

Etiology:

Sepsis can be a response to any class of microorganism. Microbial invasion of the bloodstream is not essential, since local inflammation can also elicit distant organ dysfunction and hypotension. In fact, blood cultures yield bacteria or fungi in only 20–40% of cases of severe sepsis and 40–70% of cases of septic shock. Individual gram-negative or gram-positive bacteria account for 70% of these isolates; the remainder are fungi or a mixture of microorganisms.

Pathophysiology

Most cases of severe sepsis are triggered by bacteria or fungi that do not ordinarily cause systemic disease in immunocompetent hosts . To survive within the human body, these microbes often exploit deficiencies in host defenses, indwelling catheters or other foreign matter, or obstructed fluid drainage conduits.

Microbial pathogens, in contrast, can circumvent innate defenses because they (1) lack molecules that can be recognized by host receptors or (2) elaborate toxins or other virulence factors. In both cases, the body can mount a vigorous inflammatory reaction that results in severe sepsis yet fails to kill the invaders. The septic response may also be induced by microbial exotoxins that act as superantigens (e.g., toxic shock syndrome toxin) as well as by many pathogenic viruses.

Local and Systemic Host Responses to Invading Microbes

Recognition of microbial molecules by tissue phagocytes triggers the production and/or release of numerous host molecules (cytokines, chemokines, prostanoids, leukotrienes, and others) that increase blood flow to the infected tissue, enhance the permeability of local blood vessels, recruit neutrophils to the site of infection, and elicit pain. These reactions are familiar elements of local inflammation, the body's frontline innate immune mechanism for eliminating microbial invaders. Systemic responses are activated by neural and/or humoral communication with the hypothalamus and brainstem; these responses enhance local defenses by increasing blood flow to the infected area, augmenting the number of circulating neutrophils, and elevating blood levels of numerous

molecules (such as the microbial recognition proteins discussed above) that have anti-infective functions.

Cytokines and Other Mediators

Cytokines can exert endocrine, paracrine, and autocrine effects . TNF-alpha stimulates leukocytes and vascular endothelial cells to release other cytokines to express cell-surface molecules that enhance neutrophil-endothelial adhesion at sites of infection, and to increase prostaglandin and leukotriene production. Although TNF-alpha is a central mediator, it is only one of many proinflammatory molecules that contribute to innate host defense. Chemokines, most prominently interleukin (IL)-8 and IL-17, attract circulating neutrophils to the infection site. IL-1beta exhibits many of the same activities as TNF-alpha. IFN gamma, IL-12, IL-17, and other proinflammatory cytokines probably interact synergistically with one another and with additional mediators. The nonlinearity and multiplicity of these interactions have made it difficult to interpret the roles played by individual mediators in both tissues and blood.

Coagulation Factors

Intravascular thrombosis, a hallmark of the local inflammatory response, may help wall off invading microbes and prevent infection and inflammation from spreading to other tissues. IL-6 and other mediators promote intravascular

coagulation initially by inducing blood monocytes and vascular endothelial cells to express tissue factor

CONTROL MECHANISMS

1. Local Control Mechanisms

The anti-inflammatory forces that put out the fire and clean up the battleground include molecules that neutralize or inactivate microbial signals. Among these molecules are intracellular factors (e.g., suppressor of cytokine signalling 3 and IL-1 receptor–associated kinase 3) that diminish the production of proinflammatory mediators by neutrophils and macrophages; anti-inflammatory cytokines (IL-10, IL-4); and molecules derived from essential polyunsaturated fatty acids (lipoxins, resolvins, and protectins) that promote tissue restoration.

2. Systemic Control Mechanisms

Systemic responses to infection diminish the cellular responses to microbial molecules. Circulating levels of anti-inflammatory cytokines (e.g., IL-10) increase even in patients with mild infections. Glucocorticoids inhibit cytokine synthesis by monocytes in vitro; the increase in blood cortisol levels early in the systemic response presumably plays a similarly inhibitory role. Epinephrine inhibits the TNF-alpha response to endotoxin infusion in humans while augmenting and accelerating the release of IL-10; prostaglandin E2 has a similar "reprogramming" effect on the responses of circulating monocytes to

LPS and other bacterial agonists. Cortisol, epinephrine, IL-10, and C-reactive protein reduce the ability of neutrophils to attach to vascular endothelium, favouring their demargination and thus contributing to leukocytosis while preventing neutrophil-endothelial adhesion in uninflamed organs.

It can thus be concluded that both local and systemic responses to infectious agents benefit the host in important ways. Most of these responses and the molecules responsible for them have been highly conserved during animal evolution and therefore may be adaptive. Elucidating how they contribute to lethality—i.e., become maladaptive—remains a major challenge for sepsis research.

Organ Dysfunction and Shock

As the body's responses to infection intensify, the mixture of circulating cytokines and other molecules becomes very complex: elevated blood levels of more than 50 molecules have been found in patients with septic shock. Although high concentrations of both pro- and anti-inflammatory molecules are found, the net mediator balance in the plasma of these extremely sick patients seems to be anti-inflammatory.

Endothelial Injury

Many investigators have favoured widespread vascular endothelial injury as the major mechanism for multiorgan dysfunction.

Septic Shock

The hallmark of septic shock is a decrease in peripheral vascular resistance that occurs despite increased levels of vasopressor catecholamines. Prominent hypotensive molecules include nitric oxide, beta-endorphin, bradykinin, platelet-activating factor, and prostacyclin.

The pathogenesis of severe sepsis may differ according to the infecting microbe, the ability of the host's innate defense mechanisms to sense it, the site of the primary infection, the presence or absence of immune defects, and the prior physiologic status of the host.

Clinical Manifestations

The manifestations of the septic response are superimposed on the symptoms and signs of the patient's underlying illness and primary infection. The rate at which severe sepsis develops may differ from patient to patient, and there are striking individual variations in presentation.

Major Complications

1. Cardiopulmonary Complications

Ventilation-perfusion mismatching produces a fall in arterial PO_2 early in the course. Progressive diffuse pulmonary infiltrates and arterial hypoxemia (Pa_{O2}/FI_{O2}, <300) indicate the development of acute lung injury; more severe

hypoxemia (Pa_{O2}/FI_{O2}, <200) denotes the **acute respiratory distress syndrome (ARDS).**

Sepsis-induced hypotension (see "Septic Shock," above) usually results initially from a generalized maldistribution of blood flow and blood volume and from hypovolemia that is due, at least in part, to diffuse capillary leakage of intravascular fluid.

Depression of myocardial function, manifested as increased end-diastolic and systolic ventricular volumes with a decreased ejection fraction, develops within 24 hours in most patients with severe sepsis.

2. **Renal Complications**

Oliguria, azotemia, proteinuria, and non-specific urinary casts are frequently found. Many patients are inappropriately polyuric; hyperglycemia may exacerbate this tendency. Most renal failure is due to acute tubular necrosis induced by hypotension or capillary injury.

3. **Coagulopathy**

Although thrombocytopenia occurs in 10–30% of patients, the underlying mechanisms are not understood. Platelet counts are usually very low (<50,000/microL) in patients with DIC.

4. Neurologic Complications

When the septic illness lasts for weeks or months, "critical illness" polyneuropathy may prevent weaning from ventilatory support and produce distal motor weakness. Electrophysiological studies are diagnostic. Guillain-Barre syndrome, metabolic disturbances, and toxin activity must be ruled out.

5. Immunosuppression

Patients with severe sepsis are often profoundly immunosuppressed. Manifestations include loss of delayed-type hypersensitivity reactions to common antigens, failure to control the primary infection, and increased risk for secondary infections (e.g., by opportunists such as *Stenotrophomonas maltophilia*, *Acinetobacter calcoaceticus-baumannii*, and *Candida albicans*)[8]. Increasing understanding of the various inflammatory cascade mechanisms has given new insights and provided several markers that, in conjunction with other manifestations of sepsis, can be useful as indicators of infection. C-reactive protein (CRP) is one such marker.

C-REACTIVE PROTEIN

Physiology of C-reactive protein

C-reactive protein is a long-established marker of sepsis. In 1930, Tillet and Francis identified, in the sera of patients with pneumonia, the capacity to

precipitate polysaccharide fractions, designated as fraction C, from *Streptococcus pneumoniae*[9]. This property quickly disappeared as patients recovered and was not identified in healthy volunteers. When the cause of this reaction was identified as a protein, it was named CRP. The "acute phase" designation was introduced to classify acutely ill patients with infection whose sera was CRP positive. Since then, several other acute phase proteins have been described.

C-reactive protein belongs to the pentraxin family of proteins, so called because they form a cyclic pentamer composed of five identical non-glycosylated sub-units. C-reactive protein binds to several polysaccharides and peptido-polysaccharides present in bacteria, fungi and parasites in the presence of calcium. These complexes activate the classical complement pathway, acting as opsonins and promoting phagocytosis[10]. Together with complement components, CRP is the only acute phase protein directly involved in the clearance of micro-organisms.

The serum concentration of CRP in the normal human population has a median of 0.8 mg/l (interquartile range 0.3–1.7 mg/l) and is below 10 mg/l in 99% of normal samples[11,12]. Levels above these values are abnormal and indicate the presence of a disease process.

As with many other acute phase proteins, CRP is predominantly synthesised by the liver, mainly in response to interleukin 6 (IL-6) . A good correlation exists between CRP and IL-6 levels [13]. Tumour necrosis factorα (TNFα) and IL-1 are also regulatory mediators of CRP synthesis . The secretion of CRP begins within 4–6 h of the stimulus, doubling every 8 h and peaking at 36–50 h.

Elevations in serum CRP are seen with most invasive infections[14,15] . Both acute systemic Gram-positive and Gram-negative bacterial infections, as well as systemic fungal infections cause marked CRP rises, even in immunodeficient patients. By contrast, CRP concentrations tend to be lower in most acute viral infections. Nevertheless, this rule is not absolute and uncomplicated infections with adenovirus, measles, mumps and influenza are sometimes associated with high CRP levels.

In addition to infection, there are several other conditions that commonly lead to substantial changes in CRP concentrations. These include trauma, surgery, burns, tissue necrosis, immunologically mediated inflammatory diseases, crystal-induced inflammatory diseases and advanced cancer.

CLINICAL APPLICATIONS OF C-REACTIVE PROTEIN

A. Evaluation of a single C-reactive protein determination

1. Sepsis diagnosis

The value of a single CRP measurement in sepsis diagnosis has been investigated in different clinical situations. In two recently published studies in critically ill patients, the best cut-off for the diagnosis of sepsis was 50 mg/l (sensitivity 98.5% and specificity 75%) and 79 mg/l (sensitivity 71.8%, specificity 66.6%) [16,17]

2. Disease severity

The single determinant of CRP level is its rate of synthesis, which in turn depends on the inflammatory insult intensity. In a recent study, CRP levels from each septic patient were grouped according to the ACCP/SCCM Consensus Conference classification . Mean values were 70 mg/l in systemic inflammatory response syndrome (SIRS) patients, 98 mg/l in sepsis, 145 mg/l in severe sepsis and 173 mg/l in septic shock, probably reflecting different degrees of inflammatory response [18].

3. Outcome prediction

Besides its use in the diagnosis of sepsis, CRP has also been evaluated as a prognostic marker. Non-survivors had a median CRP concentration on admission of 70 mg/l, significantly higher than that measured in survivors (18 mg/l)[19]

B. Evaluation of serial c-reactive protein determinations

There is a large body of literature dealing with clinical applications and the discriminative value of a single CRP value. However, it is more important to follow its evolution over the duration of hospital stay. Changes are very helpful in diagnosis as well as in monitoring response to therapy, as CRP levels are only determined by the rate of synthesis. In contrast, other acute phase phenomena such as leukocytosis and fever are dependent on complex mechanisms involving several mediators. Therefore, these markers are not reliable markers of sepsis.

1. Sepsis diagnosis

Infection should always be suspected if there is a steady increase in CRP levels over 2–3 days in the absence of an intervention likely to mount an inflammatory response.

2. **Response to therapy**

After the diagnosis of infection and the start of therapy, serial determinations of CRP provide important information. The value of CRP changes over time has not yet been systematically investigated, but in several papers the authors recognised that decreases in CRP levels coincide with clinical improvements while, on the other hand, CRP increases suggest infectious complications.[20,21]

In conclusion, serial CRP measurement, rather than a single determination at the time of admission, is a simple and valuable instrument in the diagnosis of sepsis and infection as well as in monitoring the response to therapy.

Other markers of infection

The classic markers of infection are fever and leukocytosis. Although economical and easy to measure, body temperature is a specific, but not sensitive, marker of infection[22,23]. The WCC count is routinely performed in almost every ICU and is also a criterion of sepsis. It is influenced by many non-infectious factors, such as acute myocardial infarction, catecholamines, corticosteroids and acute bleeding.[24]

PCT (Procalcitonin) was described more recently and is not routinely measured in all hospital laboratories. PCT levels have been shown to correlate with the severity of sepsis as measured by the acute physiology and chronic

health evaluation **(APACHE) II** or sequential organ failure assessment **(SOFA)** scores, and a recent meta-analysis reported that PCT was more sensitive and specific than CRP for differentiating bacterial from noninfective causes of inflammation. In addition, PCT is produced and cleared more rapidly than CRP, making it potentially more useful for identifying infection early and for following the progress of disease. Using a new sensitive and rapid PCT assay, Christ-Crain et al. have shown that PCT-guided therapy can reduce total antibiotic exposure and antibiotic treatment duration in patients with community-acquired pneumonia. However, further studies are needed to confirm these results and to evaluate the use of PCT levels to guide therapy in heterogeneous groups of patients. Further study is also needed to define and validate specific cut-off values in different disease states.

Clinicians using PCT as a marker of infection should be aware of some important and potentially dangerous limitations. The behaviour of PCT in acute renal failure is still unknown . In cardiac surgery patients complicated with mediastinitis, PCT concentrations were almost normal (0.8±0.58 ng/ml) in comparison with noninfected patients (0.41±0.36 ng/ml)[25]. In a study in critically ill patients, PCT was below 1.0 ng/ml in 12.5% and 62.5% of infected patients with and without septic shock, respectively [26]. Finally, in community-acquired pneumonia PCT can be normal or even undetectable (median 0.2 ng/ml, range 0.1–6.7 ng/ml, *n*=149) . There is no obvious explanation for these

unexpected findings. With regard to cost, measurement of PCT is considerably more expensive than CRP.

Elevated serum levels of the intracellular enzyme LDH in sepsis might result from various mechanisms including cellular injury related to bacterial toxins, ischemia and cytotoxic-reactive oxygen species generated during reperfusion. Various studies have confirmed the presence of elevated LDH levels in severe sepsis. There is a study in US which predicted the development of ARDS in patients in sepsis based on serum LDH levels.[27]

Prognostic Scoring Systems

The high-complexity features of intensive care unit services and the clinical situation of patients themselves render correct prognosis fundamentally important not only for patients, their families and physicians, but also for hospital administrators, fund-providers and controllers. Prognostic indices have been developed for estimating hospital mortality rates for patients hospitalised in intensive care units, based on demographic, physiological and clinical data. The most frequently used indices are **APACHE II** (Acute Physiology and Chronic Health Evaluation II), **APACHE III** (Acute Physiology And Chronic Health Evaluation III), **SAPS II** (Simplified Acute Physiology Score II) and MPM II (Mortality Probability Model II).[32,33]

The APACHE II index consists of a score that takes account of the patient's age, chronic health condition and physiological variables (internal temperature, heart rate, respiratory rate, oxygenation, arterial pH, sodium, potassium, creatinine, hematocrit, white blood cells and Glasgow coma score).

Markgraf et al.[34] compared the predictive capabilities of APACHE II, APACHE III and SAPS II and concluded that the three indices have good discriminating power and that APACHE II has the best calibration. For this reason, it scored the most accurate mortality prediction.

Over the past years many scoring models have been developed to describe the severity of illness of intensive care patients or to predict the outcome of intensive care. As an example, the first Sepsis-related Organ Failure Assessment score, later called the **Sequential Organ Failure Assessment (SOFA) score**, was introduced in 1994[35]. The aim was to quantify the severity of the patients' illness based on the degree of organ dysfunction, serially over time. Although severity of illness scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE) II and the Simplified Acute Physiology Score (SAPS)II [36]are based on the first 24 hrs of intensive care unit (ICU) admission, the SOFA scoring system takes into account the time course of a patient's condition during the entire ICU stay. This enables physicians to follow the evolving disease process. The SOFA score is composed of scores from six

organ systems, each graded from 0 to 4 points according to the degree of dysfunction. The assignment of scores for each organ system is based on one or more variables. For example, the SOFA score for renal function is derived from the serum creatinine level and urine output. Previous studies have shown that the SOFA score is suitable to evaluate organ dysfunction.

Vincent et al. [35]stated that one of the criteria for a system that defines the degree of organ dysfunction is that it should be based on a limited number of simple but objective variables that are easily and routinely measured in every institution. With a total of 12 variables, the SOFA score contains fewer variables than most other ICU severity of illness scoring systems, such as APACHE II and SAPS II.

MATERIALS AND METHODS

MATERIALS AND METHODS:

The centre of study is Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai – 3.

Study Design : Cross sectional study.

Venue : Rajiv Gandhi Government General Hospital, Chennai

Collaborating Departments :

Institute of Biochemistry, MMC&RGGGH, Ch-3

Institute of Pathology , MMC&RGGGH, Ch-3

Barnard Institute of Radiology, MMC&RGGGH, Ch-3

Institute of microbiology, MMC&RGGGH, Ch-3

Duration : Study was conducted from June 2011 to November 2011

About fifty patients who attended our outpatient or emergency department with history of fever, cough with expectoration of recent onset, vomiting, burning micturition, breathlessness, confusion , or jaundice were selected randomly. A complete history was taken either from the patient or his/ her attender including past history of jaundice, DM, hypertension, coronary artery disease, seizures, cva , COPD, h/o prior surgery, malignancy, blood transfusion and retroviral status. His/her personal habits were enquired.

A complete physical examination was done with monitoring of vitals (temperature, pulse rate, respiratory rate and blood pressure) everyday or frequently as the patient condition demanded. A battery of blood investigations were done including renal functions, liver functions test, Complete blood count, HBs Ag, HIV, Widal test, MSAT, QBC for MP, blood –culture and sensitivity, serumCRP , sr LDH, prothrombin time and Arterial Blood gas analysis. Other investigations included were Urine analysis, urine – C/S, ECG, Chest X ray, USG abdomen and if required CT-Chest and CT- Abdomen.

CBC, RFT and LFT were repeated on the third day (48-72 hrs) and APACHE-II score and SOFA score were computed on first and third day.

C-reactive protein in serum was measured **by Immunoturbidimetric Assay** using clinical chemistry analysers. Lactate dehydrogenase- P was measured using kinetic DGKC method.

Inclusion Criteria:

Patients older than 18yrs of age admitted in medical ward with criteria for sepsis ,i.e.,

Two or more of the following conditions:

1. fever (oral temperature >38°C) or hypothermia (<36°C);

2. tachypnea (>24 breaths/min);
3. tachycardia (heart rate >90 beats/min);
4. leukocytosis (>12,000/ L), leukopenia (<4,000/ L), or >10% bands; plus

proven or suspected microbial etiology

Exclusion Criteria :

1. Patients less than 18 years of age
2. Patients with rheumatic heart disease and collagen vascular disease
3. Patients with history of transient ischemic attack or cerebrovascular accident or coronary artery disease
4. Patients with chronic kidney disease

Statistical Analysis Plan :

Data analysed using statistical package - SPSS Software

Consent

All participants / attenders gave written informed consent.

Ethical Committee Approval

Institutional Ethics Committee of Madras Medical College approved the study

OBSERVATION AND RESULTS

OBSERVATION AND RESULTS:

In the study of fifty cases of sepsis admitted in Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai, the following observations were made in sex incidence, age, Erythrocyte Sedimentation Rate, serum C-reactive protein level, serum Lactate dehydrogenase level, APACHE II score within 24hours of admission and after 48-72 hrs, SOFA score within 24hours of admission and after 48-72 hrs and prognosis of the illness as follows:

Total number of patients : 50

Total number of males : 27 (54%)

Total number of females : 23 (46%)

AGE INCIDENCE:

Age incidence:

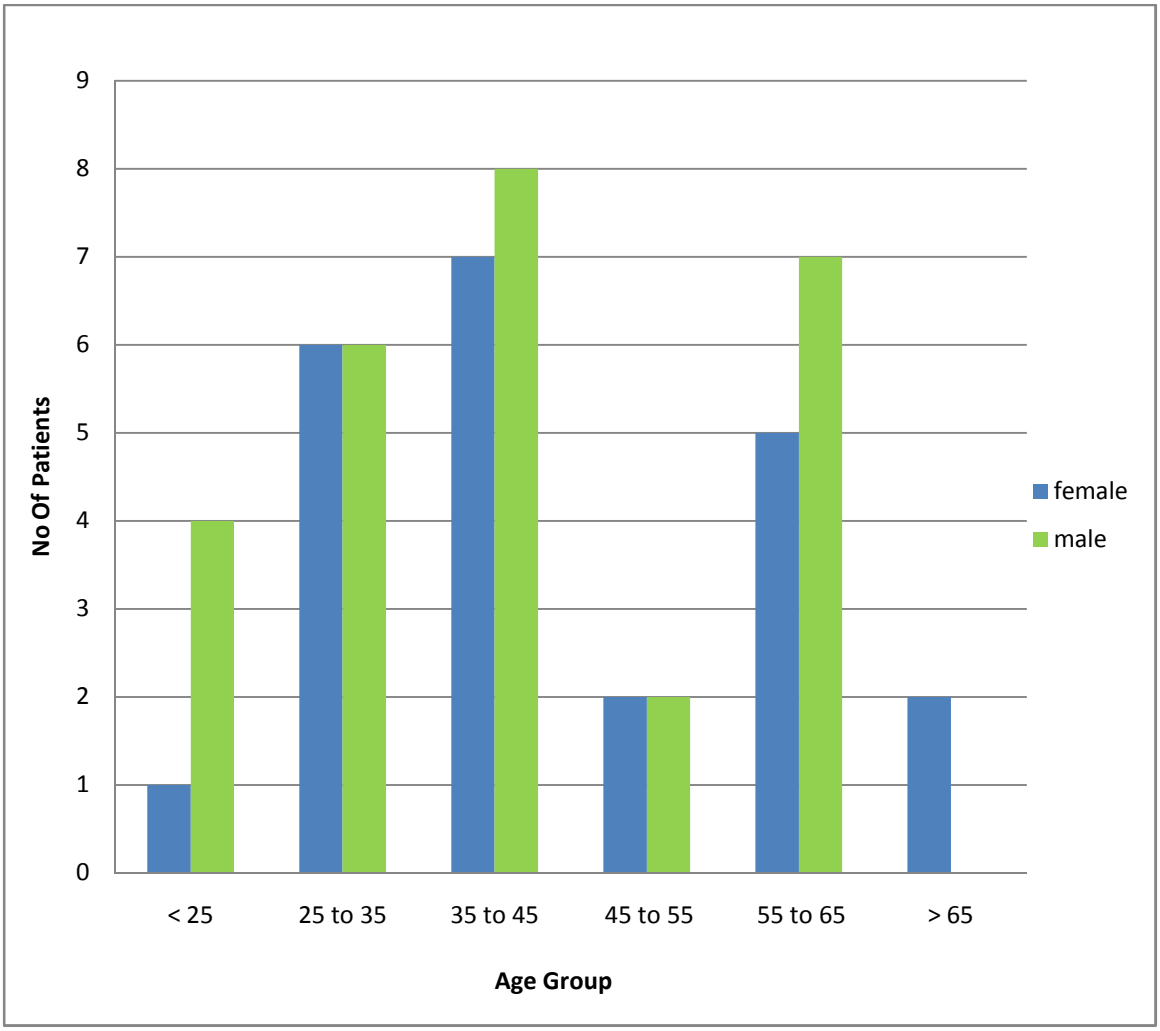
Age	Female	Male	Grand Total	Percentage
< 25	1	4	5	10%
25 to 35	6	6	12	24%
35 to 45	7	8	15	30%
45 to 55	2	2	4	8%
55 to 65	5	7	12	24%
> 65	2	0	2	4%
Grand Total	**23**	**27**	**50**	

Age average = 43.52

Age median = 42.5

Age mode = 45

Age wise Distribution



Mortality: Overall

Total number of patients : 50

Total number - survived : 37

Total number - expired : 13

Mortality percentage : 26%

Females

Total number of females : 23

Total number - survived : 18

Total number - expired : 5

Mortality percentage : 21.7%

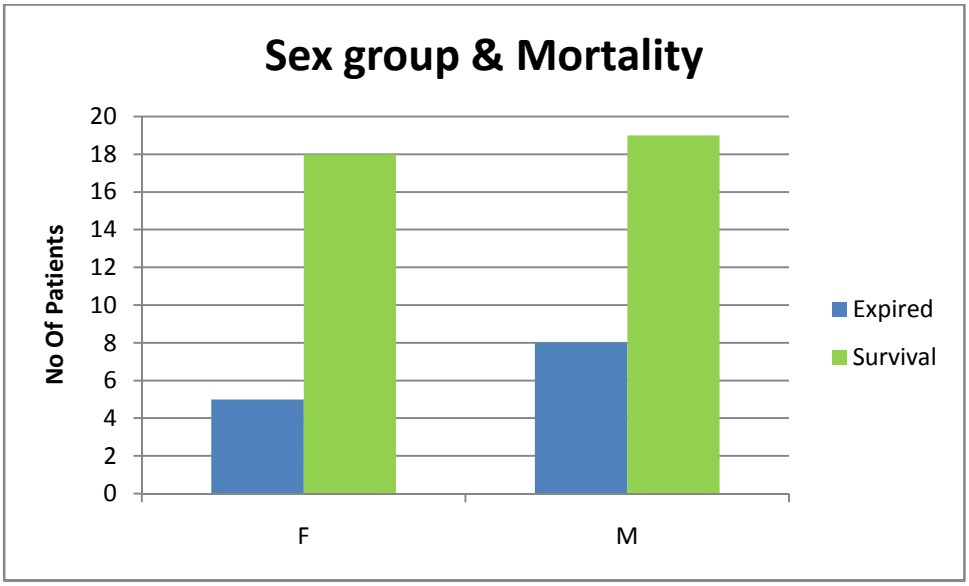
Males

Total number of males : 27

Total number - survived : 19

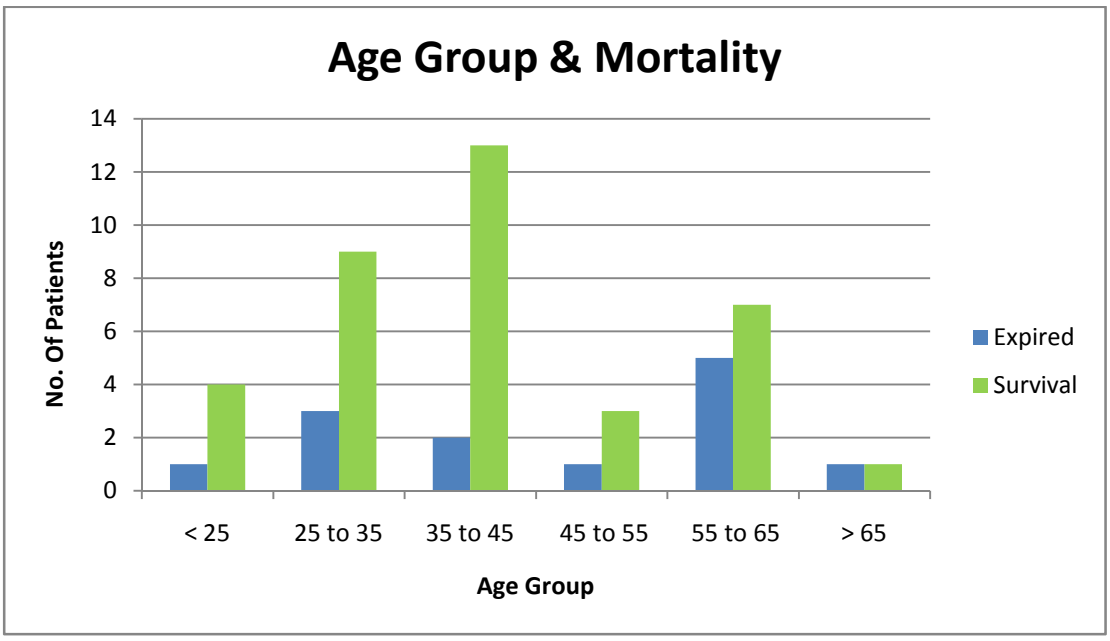
Total number - expired : 8

Mortality percentage : 29.5%



Age wise Mortality:

Age in yrs	Expired	Survival	Grand Total	Percentage
< 25	1	4	5	20%
25 to 35	3	9	12	25%
35 to 45	2	13	15	13.3%
45 to 55	1	3	4	25%
55 to 65	5	7	12	41.6%
> 65	1	1	2	50%
Grand Total	**13**	**37**	**50**	**26%**

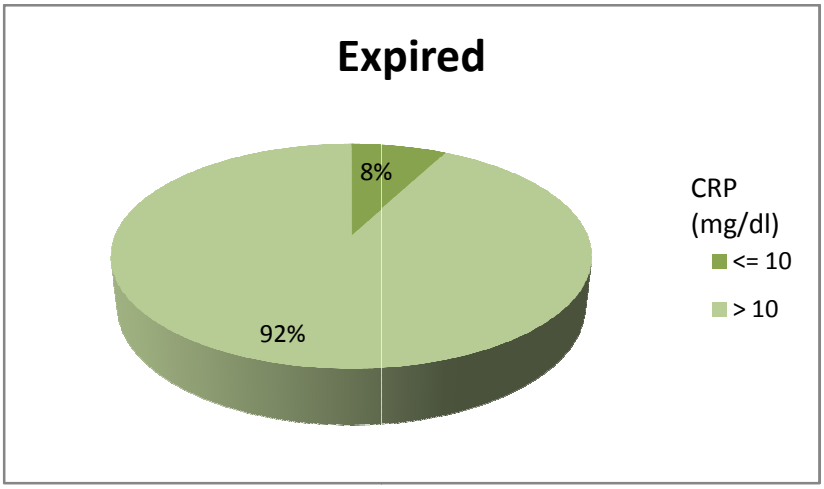


Serum CRP, LDH and Mortality :

Serum C-reactive protein, lactate dehydrogenase and ESR were done on admission and APACHE II and SOFA score were computed on day 1 (within 24 hrs) and day 3 (48-72 hrs). out of the 50 patients, 10 patients had CRP level <=10mg/dl and 40 patients had CRP level >10mg/dl.

CRP AND MORTALITY

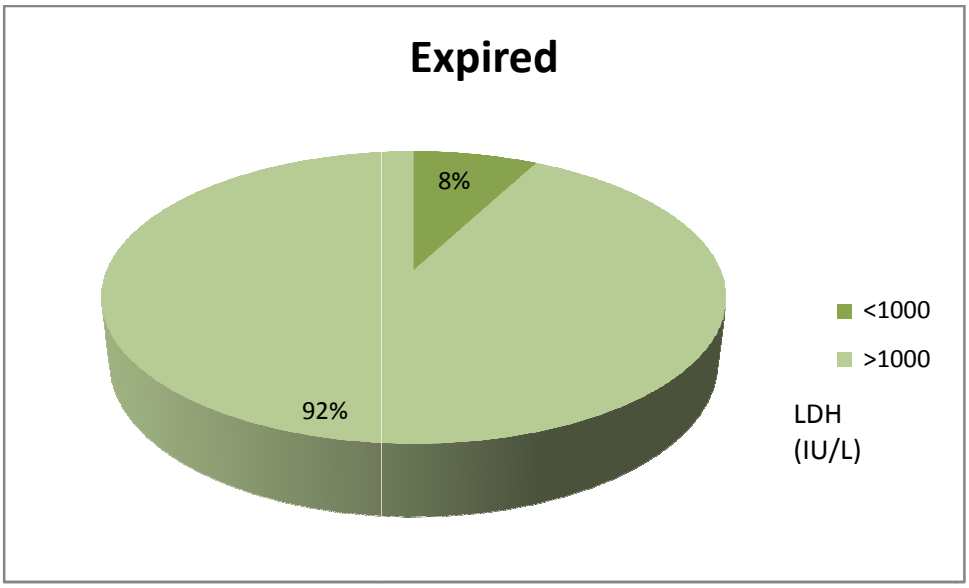
CRP (mg/dl)	Expired	Survival	Grand Total	Percentage
<= 10	1	9	10	10%
> 10	12	28	40	30%
Grand Total	**13**	**37**	**50**	**26%**



Of the 13 death patients, only one had CRP < 10mg/dl while all others had CRP > 10mg/dl.

LDH AND MORTALITY:

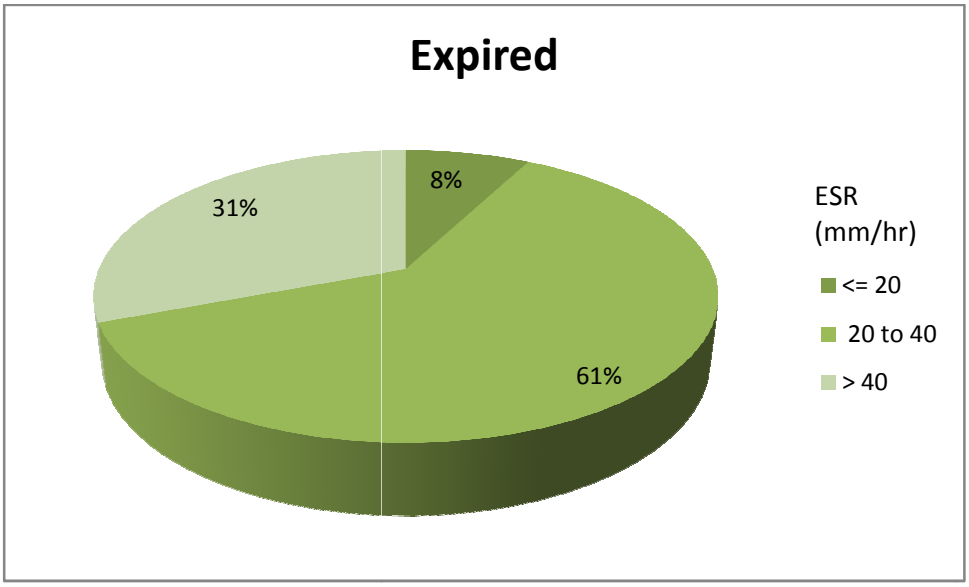
LDH (IU/L)	Expired	Survival	Grand Total	Percentage
<1000	1	30	31	3.22%
>1000	12	7	19	63.15%
Grand Total	**13**	**37**	**50**	**26%**



Of the 13 death patients, only one had LDH <= 1000 IU/L while all others had LDH > 1000 IU/L.

ESR AND MORTALITY :

ESR (mm/hr)	Expired	Survival	Grand Total	Percentage
<= 20	1	12	13	7.69%
20 to 40	8	21	29	27.59%
> 40	4	4	8	50%
Grand Total	**13**	**37**	**50**	**26%**



Of the 13 death patients, one had ESR <= 20mm/hr, eight had ESR between 20 and 40 mm/hr and four had ESR > 40mm/hr.

Serum CRP, LDH and Prognosis:

Before going into the analysis of serum CRP, LDH and ESR with prognosis, first we will look into the correlation between CRP, LDH and ESR and smoking, alcohol, hypertension and diabetes mellitus.

CRP vs Smoking

	Smoking		
CRP (mg/dl)	**Yes**	**No**	**Grand Total**
<= 10	1	9	10
> 10	8	32	40
Grand Total	**9**	**41**	**50**

p=0.66 **NOT SIGNIFICANT**

The correlation between smoking and CRP levels was not statistically significant.

CRP vs Alcohol

	Alcohol		
CRP (mg/dl)	**Yes**	**No**	**Grand Total**
<= 10	1	9	10
> 10	7	33	40
Grand Total	**8**	**42**	**50**

p=0.08 **NOT SIGNIFICANT**

The correlation between alcohol and CRP levels was not statistically significant.

CRP vs Hypertension

	Hypertension		
CRP (mg/dl)	**Yes**	**No**	**Grand Total**
<= 10	0	10	10
> 10	3	37	40
Grand Total	**3**	**47**	**50**

p=0.45 **NOT SIGNIFICANT**

The correlation between hypertension and CRP levels was not statistically significant.

CRP vs Diabetes mellitus

	Diabetes mellitus		
CRP (mg/dl)	**Yes**	**No**	**Grand Total**
<= 10	3	7	10
> 10	14	26	40
Grand Total	**17**	**33**	**50**

p=0.99 **NOT SIGNIFICANT**

The correlation between Diabetes mellitus and CRP levels was not statistically significant.

LDH vs Smoking

	Smoking		
LDH (IU/L)	**Yes**	**No**	**Grand Total**
<1000	4	27	31
>1000	5	14	19
Grand Total	**9**	**41**	**50**

p=0.28 **NOT SIGNIFICANT**

The correlation between smoking and LDH levels was not statistically significant .

LDH vs Alcohol

	Alcohol		
LDH (IU/L)	**Yes**	**No**	**Grand Total**
<1000	5	26	31
>1000	3	16	19
Grand Total	**8**	**42**	**50**

p=1.00 **NOT SIGNIFICANT**

The correlation between smoking and LDH levels was not statistically significant .

LDH vs Hypertension

	Hypertension		
LDH (IU/L)	**Yes**	**No**	**Grand Total**
<1000	0	31	31
>1000	3	16	19
Grand Total	**3**	**47**	**50**

P = 0.06 **NOT SIGNIFICANT**

The correlation between hypertension and LDH levels was not statistically significant.

LDH vs Diabetes mellitus

	Diabetes mellitus		
LDH (IU/L)	**Yes**	**No**	**Grand Total**
<1000	7	24	31
>1000	10	9	19
Grand Total	**17**	**33**	**50**

P = 0.03 **SIGNIFICANT**

The correlation between Diabetes mellitus and LDH levels was statistically significant.

ESR vs Smoking

	Smoking		
ESR (min/hr)	**Yes**	**No**	**Grand Total**
<= 20	1	12	13
20 to 40	7	22	29
> 40	1	7	8
Grand Total	**9**	**41**	**50**

P = 0.41 **NOT SIGNIFICANT**

The correlation between smoking and ESR values was not statistically significant.

ESR vs Alcohol

	Alcohol		
ESR (mm/hr)	**Yes**	**No**	**Grand Total**
<= 20	1	12	13
20 to 40	6	23	29
> 40	1	7	8
Grand Total	**8**	**42**	**50**

P = 0.61 **NOT SIGNIFICANT**

The correlation between alcohol and ESR values was not statistically significant.

ESR vs Diabetes mellitus

	Diabetes mellitus		
ESR (mm/hr)	**Yes**	**No**	**Grand Total**
<= 20	3	10	13
20 to 40	12	17	29
> 40	2	6	8
Grand Total	**17**	**33**	**50**

P = 0.45 **NOT SIGNIFICANT**

The correlation between Diabetes mellitus and ESR values was not statistically significant.

ESR vs Hypertension

	Hypertension		
ESR (mm/hr)	**Yes**	**No**	**Grand Total**
<= 20	0	13	13
20 to 40	3	26	29
> 40	0	8	8
Grand Total	**3**	**47**	**50**

P = 0.34 **NOT SIGNIFICANT**

The correlation between hypertension and ESR values was not statistically significant.

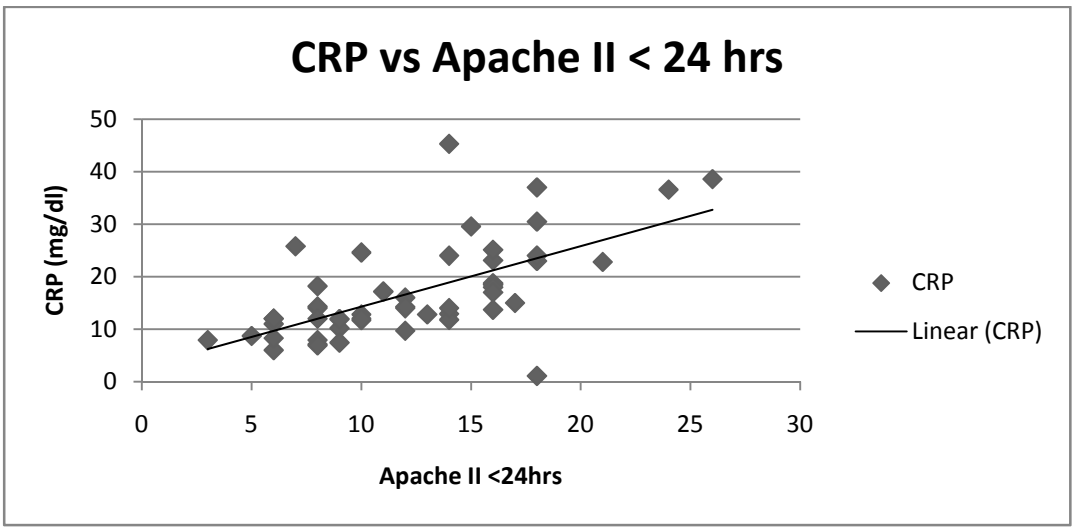
Comparison of sr CRP and prognosis :

Serum CRP on admission was compared with APACHE II score on admission and after 48 hours and also with SOFA score on admission and after 48 hours . The details are given below:

CRP vs Apache II < 24 hrs

	Apache II<24 hrs		
CRP (mg/dl)	**<=10**	**> 10**	**Grand Total**
<= 10	8	2	10
> 10	14	26	40
Grand Total	**22**	**28**	**50**

P = 0.01 **SIGNIFICANT**

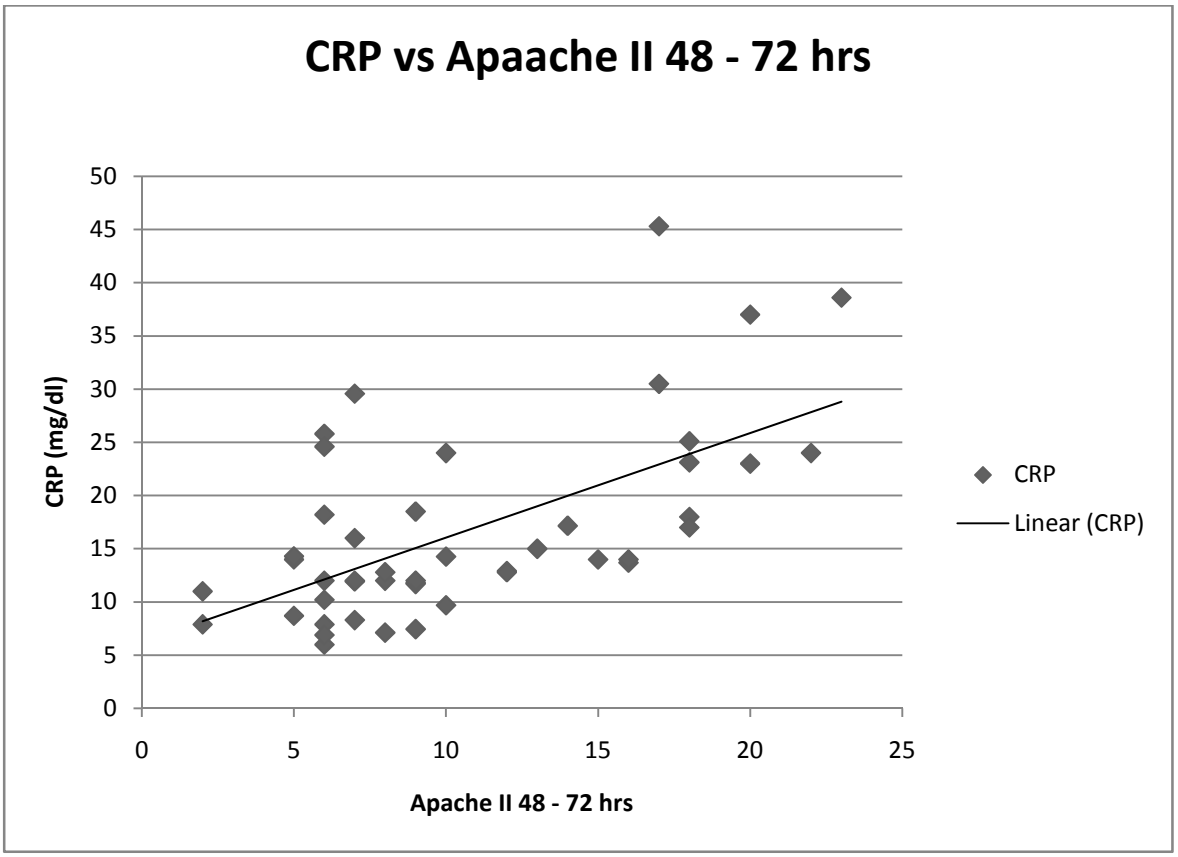


Correlation coefficient = 0.63

CRP vs Apaache II 48 - 72 hrs

	Apache II 48-72hrs		
CRP	**<=10**	**> 10**	**Grand Total**
<= 10	9	1	10
> 10	20	20	40
Grand Total	**29**	**21**	**50**

P = 0.01 **SIGNIFICANT**

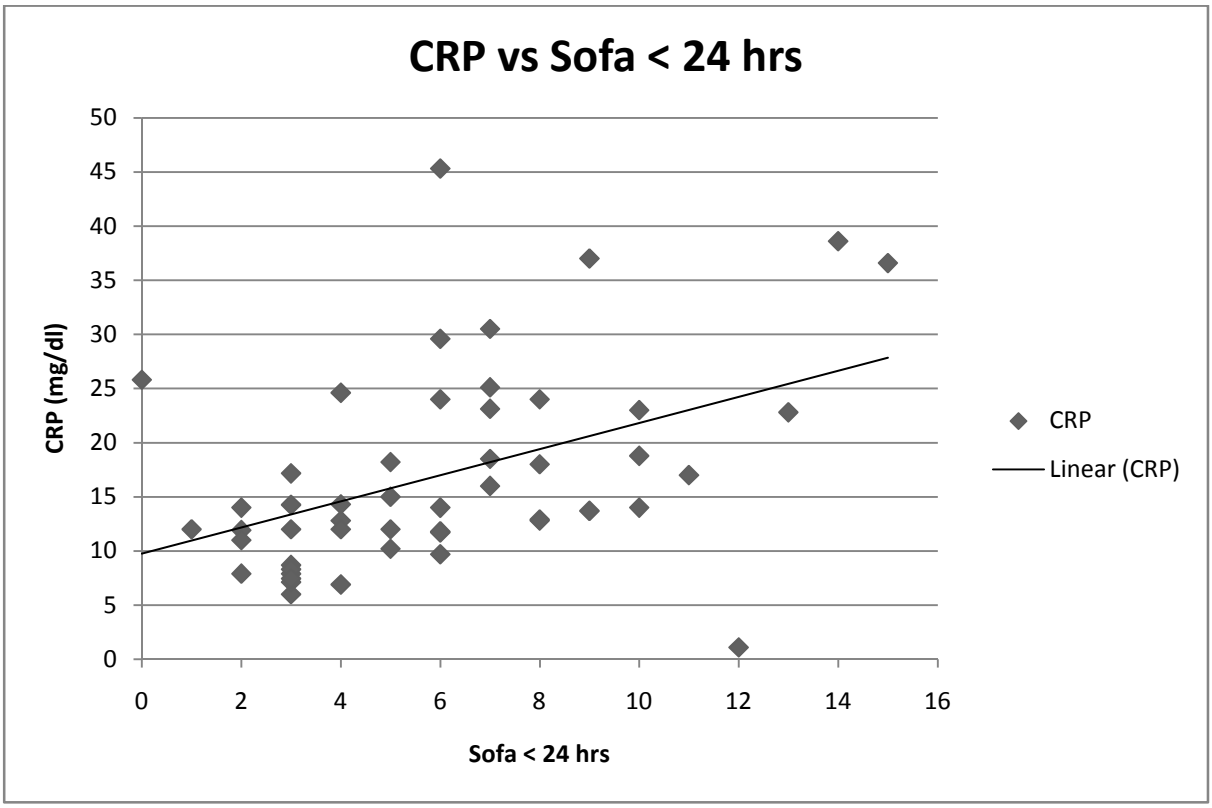


Correlation coefficient = 0.61

CRP vs Sofa < 24 hrs

	SOFA < 24hrs		
CRP(mg/dl)	**<=7**	**>7**	**Grand Total**
<= 10	9	1	10
> 10	27	13	40
Grand Total	**36**	**14**	**50**

P = 0.07 **NOT SIGNIFICANT**

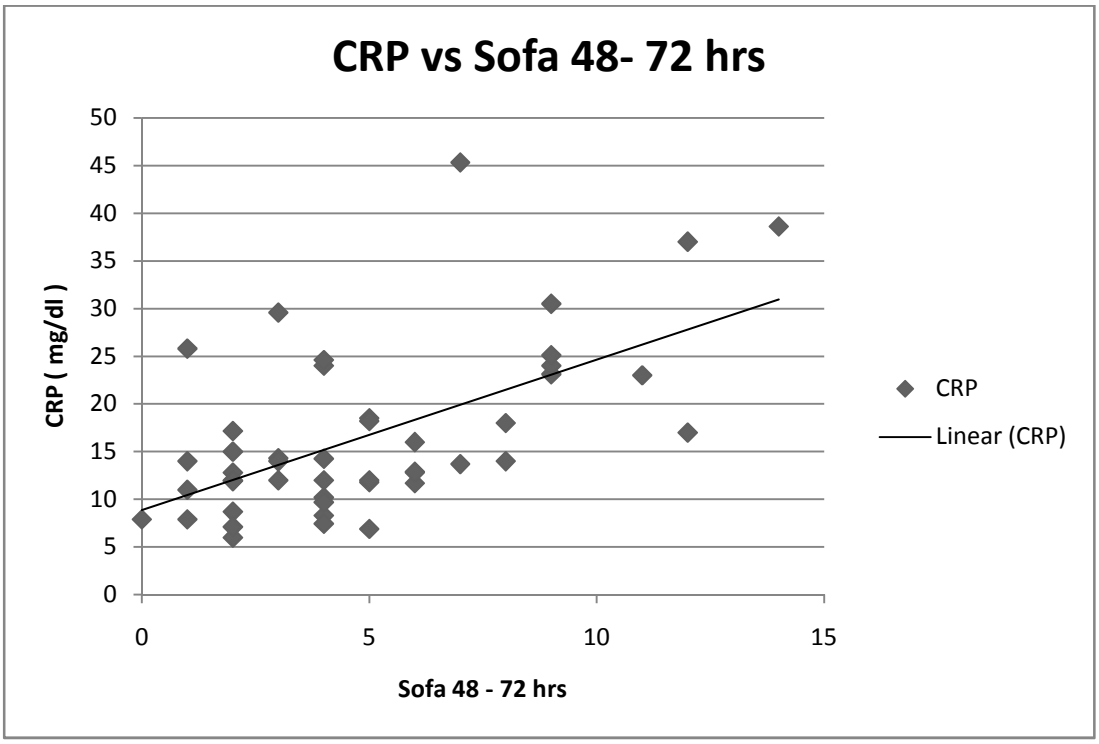


Correlation coefficient = 0.45

CRP vs Sofa 48- 72 hrs

	SOFA 48-72hrs		
CRP(mg/dl)	**<=7**	**>7**	**Grand Total**
<= 10	9	1	10
> 10	27	13	40
Grand Total	**36**	**14**	**50**

P = 0.07 **NOT SIGNIFICANT**



Correlation coefficient = 0.59

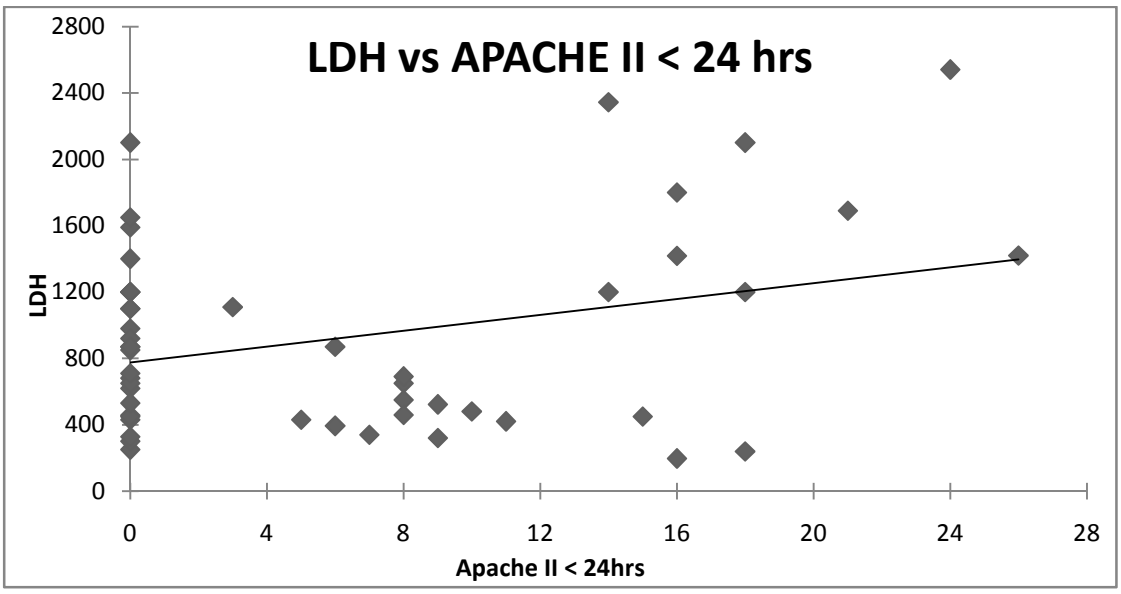
Comparison of sr LDH and prognosis :

Serum LDH on admission was compared with APACHE II score on admission and after 48 hours and also with SOFA score on admission and after 48 hours . The details are as follows:

LDH vs APACHE II < 24 hrs

	Apache II <24hrs		
LDH (IU/L)	**<=10**	**> 10**	**Grand Total**
<1000	19	12	31
>1000	3	16	19
Grand Total	**22**	**28**	**50**

P = 0.003 **SIGNIFICANT**

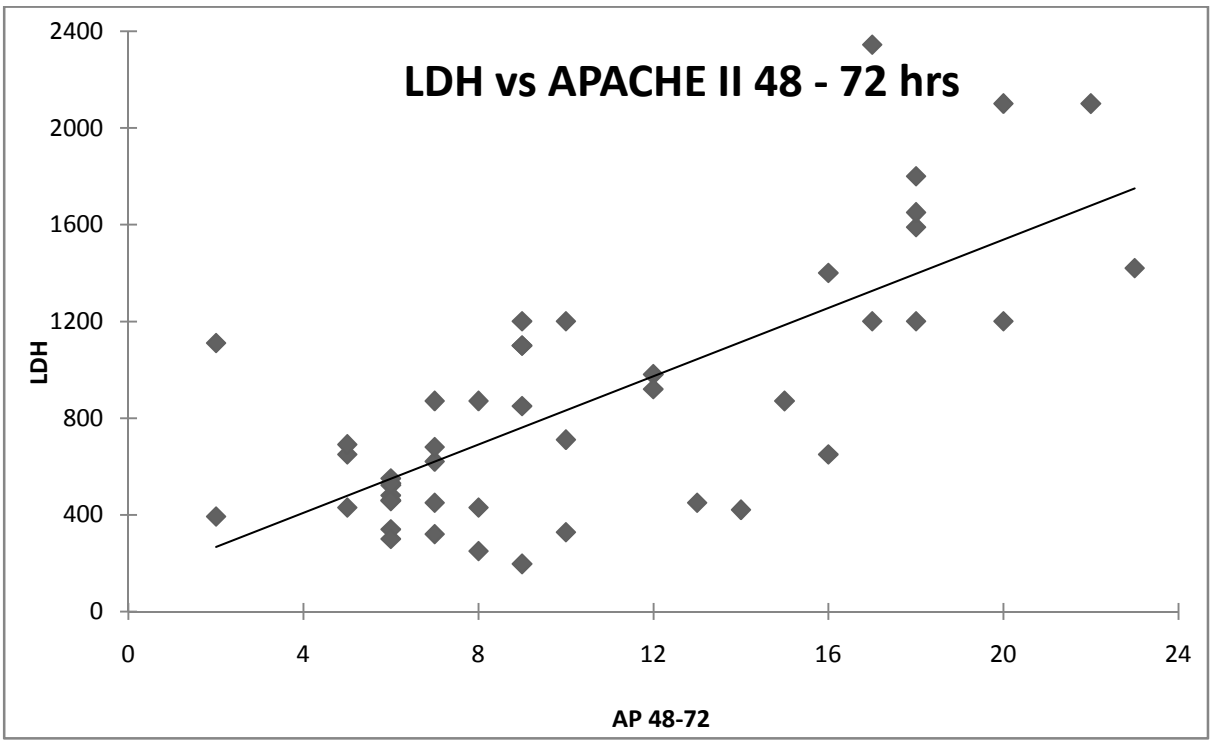


Correlation coefficient = 0.58

LDH vs APACHE II 48 - 72 hrs

	Apache II 48-72 hrs		
LDH (IU/L)	**<=10**	**> 10**	**Grand Total**
<1000	24	7	31
>1000	5	14	19
Grand Total	**29**	**21**	**50**

P = 0.001 **SIGNIFICANT**

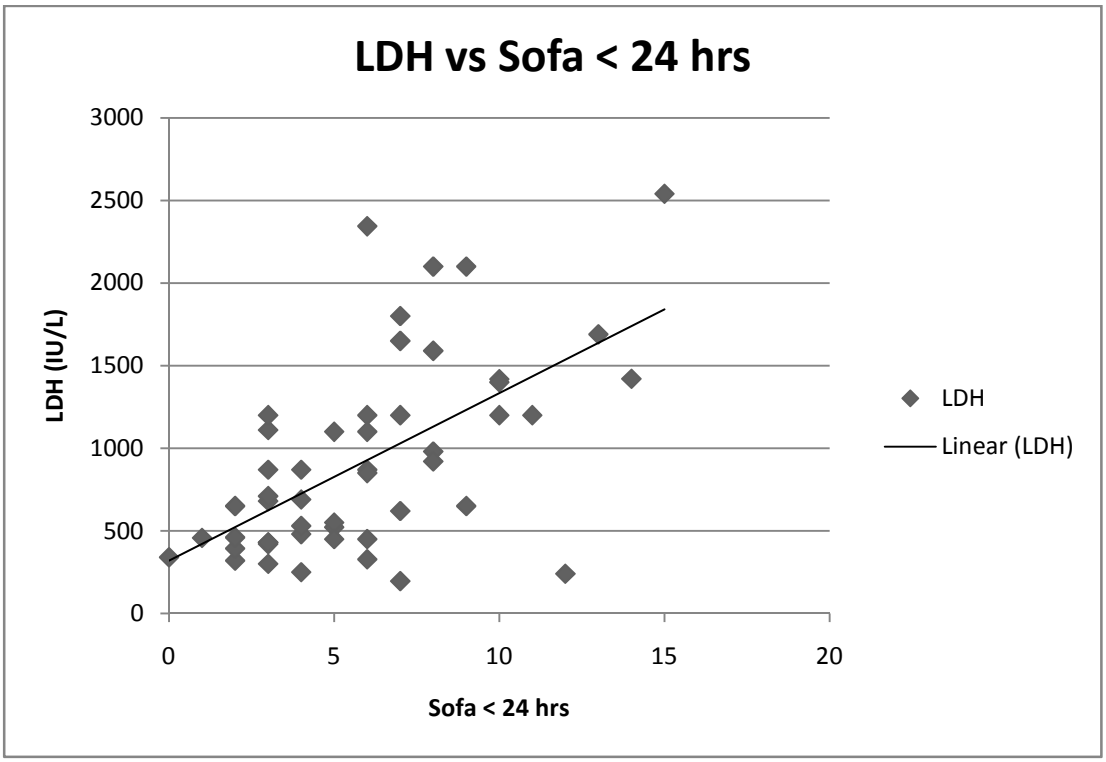


Correlation coefficient = 0.73

LDH vs Sofa < 24 hrs

SOFA <24 hrs			
LDH (IU/L)	**<=7**	**>7**	**Grand Total**
<1000	27	4	31
>1000	9	10	19
Grand Total	**36**	**14**	**50**

P = 0.002 **SIGNIFICANT**

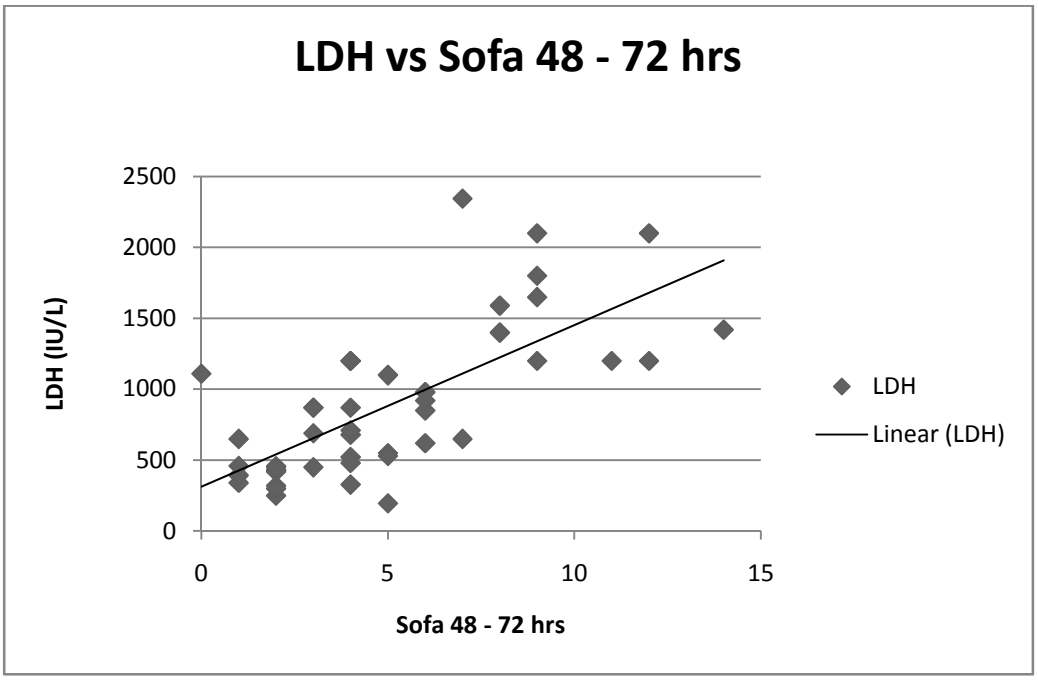


Correlation coefficient = 0.59

LDH vs Sofa 48 - 72 hrs

	SOFA 48-72hrs		
LDH (IU/L)	**<=7**	**>7**	**Grand Total**
<1000	30	1	31
>1000	6	13	19
Grand Total	**36**	**14**	**50**

P = 0.00001 **SIGNIFICANT**

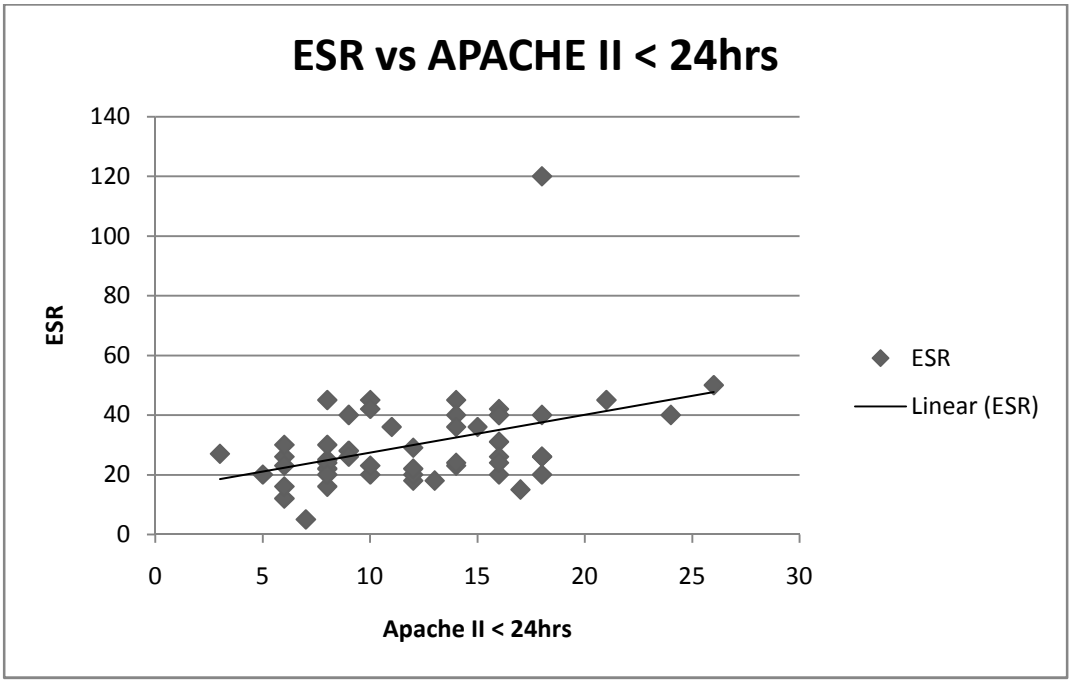


Correlation coefficient = 0.71

ESR vs APACHE II < 24hrs

	Apache II<24 hrs		
ESR (mm/hr)	**<=10**	**> 10**	**Grand Total**
<= 20	7	6	13
20 to 40	12	17	29
> 40	3	5	8
Grand Total	**22**	**28**	**50**

P = 0.07 **NOT SIGNIFICANT**

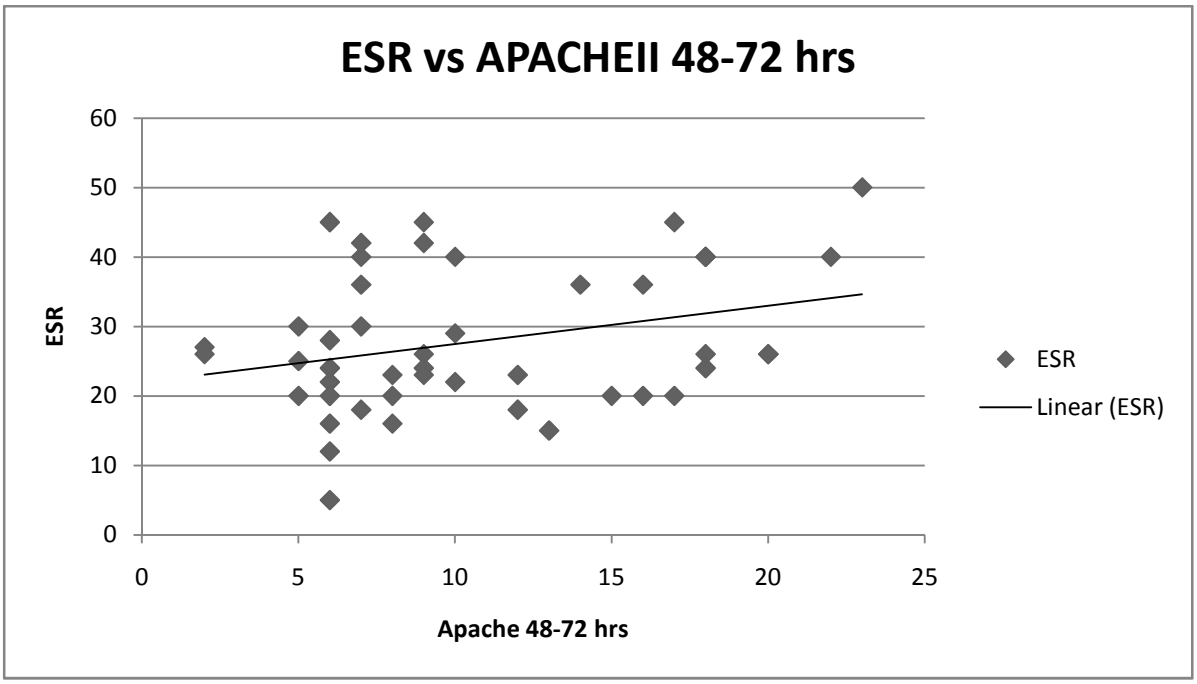


Correlation coefficient = 0.39

ESR vs APACHE II 48-72 hrs

	Apache 48-72 hrs		
ESR(mm/hr)	**<=10**	**> 10**	**Grand Total**
<= 20	8	5	13
20 to 40	17	12	29
> 40	4	4	8
Grand Total	**29**	**21**	**50**

P = 0.99 **NOT SIGNIFICANT**

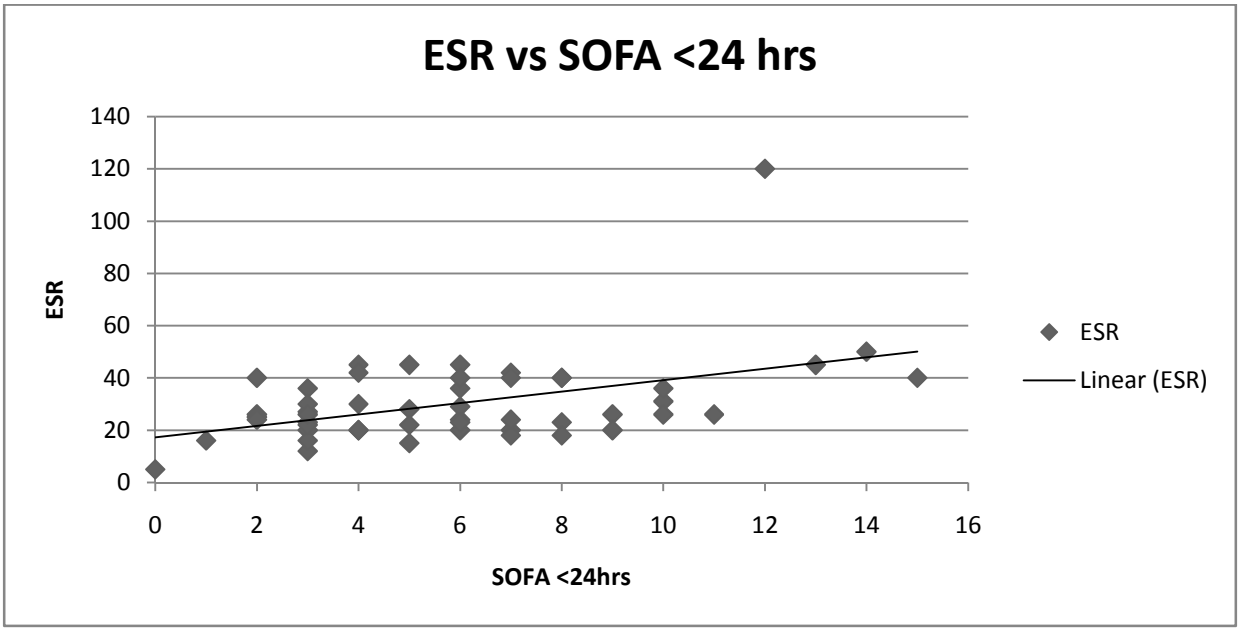


Correlation coefficient = 0.29

ESR vs SOFA <24 hrs

	SOFA <24 hrs		
ESR (mm/hr)	**<=7**	**>7**	**Grand Total**
<= 20	11	2	13
20 to 40	20	9	29
> 40	5	3	8
Grand Total	**36**	**14**	**50**

P = 0.48 **NOT SIGNIFICANT**

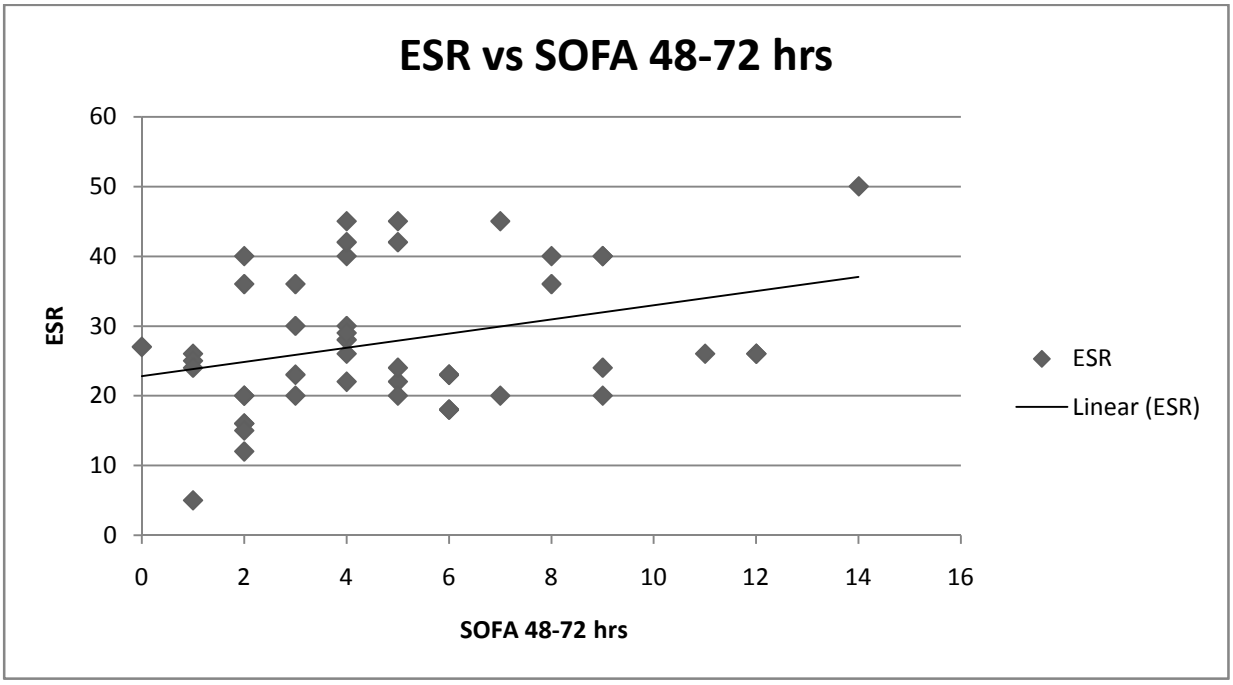


Correlation coefficient = 0.45

ESR vs SOFA 48-72 hrs

	SOFA 48 - 72hrs		
ESR (mm/hr)	**<=7**	**>7**	**Grand Total**
<= 20	12	1	13
20 to 40	19	10	29
> 40	5	3	8
Grand Total	**36**	**14**	**50**

P = 0.42 **NOT SIGNIFICANT**



Correlation coefficient = 0.33

	APACHE II <24HRS	APACHE II 48-72 HRS	SOFA <24HRS	SOFA 48-72 HRS
ESR (mm/hr)	P =0.07	P =0.99	P =0.48	P =0.42
	CC =0.39	CC =0.29	CC =0.45	CC =0.33
CRP (mg/dl)	P =0.01	P =0.01	P =0.07	P =0.07
	CC =0.63	CC =0.61	CC =0.45	CC =0.59
LDH (IU/L)	P =0.03	P =0.001	P =0.002	P =0.00001
	CC =0.58	CC =0.73	CC =0.59	CC =0.71

CC = Correlation coefficient

Sensitivity, Specificity and Positive Predictive Value Estimation for sr CRP :

CRP (mg/dl)	**ApacheII <24 hrs >10**	**ApacheII <24 hrs <=10**	**Grand Total**
> 10	26	14	40
<= 10	2	8	10
Grand Total	**28**	**22**	**50**

Sensitivity = TP/(TP + FN) * 100

= 26/28 * 100

= 92.85%

Specificity = TN/(TN+FP) * 100

= 36.36%

PPV = TP/(TP+FP) * 100

= 65%

NPV = TN/ (TN+ FN)* 100

= 80%

Sensitivity, Specificity and Positive Predictive Value Estimation for sr LDH:

	Apache II<24hrs		
LDH (IU/L)	**> 10**	**<=10**	**Grand Total**
>1000	16	3	19
<1000	12	19	31
Grand Total	**28**	**22**	**50**

Sensitivity = TP/(TP + FN) * 100

= 16/28 * 100

= 57.14%

PPV = TP/(TP+FP) * 100

= 84.21%

Specificity = TN/(TN+FP) * 100

= 86.36%

NPV = TN/ (TN+ FN) * 100

= 19/31 * 100

= 61.29%

When combining sr CRP <= 10mg/dl and sr LDH <=1000 IU/L , negative predictive value of the test for prognosis is 100%.

When combining sr CRP > 10mg/dl and sr LDH >1000 IU/L , positive predictive value of the test for prognosis is 87.5%.

DISCUSSION

DISCUSSION:

CRP is a marker of inflammation that has been used to monitor the course of infection and inflammatory diseases. Recently, CRP has been seen not only as a biochemical marker of inflammation but also as an active modulator of the inflammatory response. In this context, we evaluated ***the correlation of CRP and LDH levels with organ failure and mortality*** early after admission in a heterogeneous group of patients. We found that increased CRP concentrations were associated with organ failure, prolonged intensive care and high infection and mortality rates. CRP concentrations > 10 mg/dL and LDH >1000 IU/L on admission were associated with a particularly high mortality.

Evaluating changes in variables over time may be very helpful to assess the effects of interventions, as has been shown for organ dysfunction scoring systems. ***Lopes Ferreira et al***[28] reported that an increase in SOFA score during the first 48 hours in the ICU predicts a mortality rate of at least 50%, while a decreasing SOFA score is associated with a decrease in mortality rates from 50 to 27%. In patients with sepsis, ***Presterl et al***[29] demonstrated a correlation between the plasma levels of CRP, IL-6 and tumor necrosis factor-sR, and the APACHE III and mortality probability model II scores. Both scoring systems,

as well as CRP levels, were significantly higher in the nonsurvivors compared with the survivors. Nonsurvivors had significantly higher CRP levels from day 3 onwards. Our findings on the relation between the concentrations of CRP and APACHE II and SOFA scores indicate that both these parameters are useful indicators of severity and prognosis.

Bonig et al[30] reported that CRP levels > 10 mg/dL were predictive of poor outcome after hematopoietic stem cell transplantation in children. Chronic inflammation plays a role in the pathogenesis of cardiovascular diseases and elevated serum levels of CRP are associated with an increased risk of myocardial infarction and sudden cardiac death in apparently healthy subjects. Zimmermann et al [31] reported that high CRP levels in hemodialysis patients were closely related to high levels of vascular atherogenic risk factors and cardiovascular deaths. Serum concentrations of CRP and IL-6 have been shown to be inversely related to renal function in the predialytic phase of renal failure. In the present study, high CRP levels and high LDH levels at admission were associated with more days of receiving extracorporeal support.

In our study, the overall mortality was 26% .The mortality rate in males was 29.5% and in females was 21.7%. The mortality rate increased with increasing age and it was 41.6% in patients with age group 55-65 years and 50% in patients with age >65 years of age.

Comparison of Age, CRP, LDH, Apache II and Sofa scores between expired and survived patients

	Expired	**Survived**
No of Patients	13	37
Age	47.07	42.27
CRP	25.98 $\pm$ 11.64	13.77 $\pm$ 5.64*
LDH	1591 $\pm$ 601.5	691.4 $\pm$ 359.54*
Apache II<24 hrs	18.38 $\pm$ 3.4	10.16 $\pm$ 3.59*
Sofa <24 hrs	10 $\pm$ 2.86	4.54 $\pm$ 2.28*

*P <0.05 (T test)

The mortality rate in patients with serum CRP > 10 mg/dl was 30% while the mortality rate in patients with serum CRP < 10 mg/dl was 10%. The patients with serum CRP > 10 mg/dl also had prolonged hospital stay and multiple organ dysfunctions.

In our study, the number of patients with serum CRP < 10 mg/dl was 10 and with serum CRP > 10 mg/dl was 40. In the srCRP < 10 mg/dl group, the mean

ApacheII score on admission was 8.3 and after 48 hours was 6.55. The mean SOFA score on admission was 4.3 and after 48 hours was 3. In the srCRP > 10 mg/dl group, the mean ApacheII score on admission was 13.3 and after 48 hours was 11.64. The mean SOFA score on admission was 6.4 and after 48 hours was 5.57.This is consistent with other studies which used serum CRP as a prognostic marker in sepsis such as

Lopez et al,2011 [37]

Castelli *et al ,2004*[38]

Loboet al,2003 [39]

Comparison of Age, Apache II and Sofa scores between the two CRP groups

	CRP <= 10 mg/dl	**CRP > 10 mg/dl**
No of Patients	10	40
Age	42.5	43.775
Apache II<24 hrs	8.3 ± 3.34	13.3 ± 4.79*
Apache II 48 - 72 hrs	6.55 ± 2.35	11.64 ± 5 .86*
SOFA < 24 hrs	4.2 ± 2.94	6.4 ± 3.52
SOFA 48 -72 hrs	3 ± 1.66	5.57± 3.39*

*P <0.05 (T test)

The mortality rate in patients with serum LDH > 1000 IU/L was 63.15% while the mortality rate in patients with serum LDH < 1000 IU/L was 3.22%. The patients with serum LDH > 1000 IU/L also had prolonged hospital stay and multiple organ dysfunctions as evident from SOFA score.

In our study, the number of patients with serum LDH < 1000 IU/L was 31 and with serum LDH > 1000 IU/L was 19. In the sr LDH < 1000 IU/L group, the mean ApacheII score on admission was 8.3 and after 48 hours was 6.55. The mean SOFA score on admission was 4.3 and after 48 hours was 3. In the srLDH > 1000 IU/L group, the mean ApacheII score on admission was 13.3 and after 48 hours was 11.64. The mean SOFA score on admission was 6.4 and after 48 hours was 5.57.This is consistent with other studies which used serum LDH as a prognostic marker in sepsis such as

J.G. Zein et al, 2004 [40]

Comparison of Age, Apache II and Sofa scores between the two LDH groups

	LDH <= 1000IU/L	**LDH > 1000IU/L**
No of Patients	31	19
Age	43.58	43.4
Apache II <24 hrs	10.19 $\pm$ 3.6	15.73 $\pm$ 5.28*
Apache II 48 - 72 hrs	8.13 $\pm$ 3.3	15.37 $\pm$ 5.8*
SOFA < 24 hrs	4.51 $\pm$ 2.57	8.3 $\pm$ 3.36*
SOFA 48 -72 hrs	3.4 $\pm$ 1.75	7.5 $\pm$ 3.61*

*P <0.05 (T test)

The study showed significant correlation between serum Lactate dehydrogenase and diabetes mellitus which has been seen in studies such as " ***Activity of blood serum lactate dehydrogenase in diabetes mellitus"*** 1977 May-Jun;23(3):15-7.[41]

Serum CRP levels correlated well with the APACHE II score at admission and after 48 hours but had poor correlation with SOFA score. On the other hand, serum LDH had good correlation with both APACHE II score and SOFA score at admission and after 48 hours. However, further studies are required to confirm or repute these findings.

LIMITATIONS OF STUDY

LIMITATIONS OF STUDY:

1. We found that in our study there were some limitations with the sample size which precluded us from getting statistical significance with regard to certain variables with the severity of sepsis.

2. In our study, serum CRP and LDH levels were measured at the time of presentation and were not measured serially due to financial constraints and hence could not follow its evolution over the duration of hospital stay. Changes are very helpful in diagnosis as well as in monitoring response to therapy, as CRP levels are only determined by the rate of synthesis.

3. We had some confounding effect of Diabetes mellitus on serum Lactate dehydrogenase values which could not be corrected.

CONCLUSION

CONCLUSION :

1. Determination of CRP is an economical, consistent and reproducible test and is available in almost every hospital.

2. Serum CRP has been found to be significantly elevated with increasing severity of SEPSIS which could lead to increased predisposition to morbidity and mortality.

3. Serum Lactate Dehydrogenase level has been found to be significantly elevated with increasing severity of SEPSIS which could lead to increased predisposition to morbidity and mortality. Further studies are needed.

4. ESR is not a good prognostic marker for sepsis.

5. Combining srLDH and srCRP values has better positive value and negative predictive value than either of the two when used individually.

6. Mortality of sepsis increases with the age of the patient .

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40. Prognostic Significance of Elevated Serum Lactate Dehydrogenase (LDH) in Patients with Severe Sepsis - Joe G. Zein, MD*, Gregory L. Lee, RN, Maroun Tawk, MD, Mohammed Dabaja, MD and Gary T. Kinasewitz, MD – ICU DIAGNOSTICS AND THERAPEUTICS - Wednesday, October 27, 2004

41. Elevation of alkaline phosphotase and related enzymes in diabetes mellitus – Clinical Biochemistry, Volume 10,1977, Pages 8 -11

ANNEXURE

- PROFORMA
- MASTER CHART
- INSTITUTIONAL ETHICS COMMITTEE CERTIFICATE OF APPROVAL

SERUM LACTATE DEHYDROGENASE AND C REACTIVE PROTEIN LEVEL IN SEPSIS AND ITS CORRELATION WITH APACHE-II SCORE

PROFORMA

S. No.

Name : Age: Sex:

Occupation:

Contact No.:

Hospital No.:

Symptoms:

- Fever
- Cough with expectoration
- Jaundice
- Vomiting
- Breathlessness
- Burning micturation
- Seizures
- Altered sensorium
- Bleeding tendencies

PAST HISTORY

- Jaundice
- Surgery
- Blood transfusion

- Diabetes mellitus
- Hypertension
- Chronic liver disease
- Malignancy
- Retroviral status

v) PERSONAL HISTORY

- Alcohol
- Smoking
- Drug abuse
- Marital Status
- Promiscuity

EXAMINATION

Signs:

Consciousness : Orientation :

Clubbing :

Pallor : Y/ N Cyanosis :

Jaundice : Y / N Pedal edema :

Lymphadenopathy : JVP :

Skin – petechia or purpura : Y / N

Vital signs :

Temperature :

Respiratory rate:

Pulse :

Blood pressure:

Systemic examination :

CVS :

RESPIRATORY SYSTEM:

ABDOMEN :

CNS:

GCS:
Neck stiffness: Y/N

INVESTIGATIONS
1. Complete Hemogram

Hb%	Platelets
TC	ESR
DC	Hematocrit

2. Urine analysis

3. Blood sugar

4 Serum creatinine Blood urea
Urine output
5. Serum Na Serum K
6. Liver function tests

T. Bilirubin :	SAP :
D. Bilirubin :	T. Protein :
ID. Bilirubin :	Albumin :
AST :	
ALT :	

7. PT / INR :
8. ECG
9. X- ray chest
10.Blood C/S
11.Urine C/S (if necessary)
12. Sputum C/S
13. MSAT WIDAL QBC for MP
14. Ultrasound abdomen
15. CT Chest if necessary
16. Arterial blood gas analysis
17. PaO2

18. CRP level LDH level

19. HbsAg AntiHCV antibodies

Day 0	Day2

ACUTE PHYSIOLOGY SCORE									
Score	**4**	**3**	**2**	**1**	**0**	**1**	**2**	**3**	**4**
Rectal temperature, °C	≥41	39.0–40.9		38.5–38.9	36.0–38.4	34.0–35.9	32.0–33.9	30.0–31.9	≤29.9
Mean blood pressure, mmHg	≥160	130–159	110–129		70–109		50–69		≤49
Heart rate	≥180	140–179	110–139		70–109		55–69	40–54	≤39
Respiratory rate	≥50	35–49		25–34	12–24	10–11	6–9		≤5
Arterial pH	≥7.70	7.60–7.69		7.50–7.59	7.33–7.49		7.25–7.32	7.15–7.24	<7.15
Oxygenation									
If FI_{O_2} > 0.5, use (A – a) D_{O_2}	≥500	350–499	200–349		<200				
If FI_{O_2} ≤ 0.5, use Pa_{O_2}					>70	61–70		55–60	<55
Serum sodium, meq/L	≥180	160–179	155–159	150–154	130–149		120–129	111–119	≤110
Serum potassium, meq/L	≥7.0	6.0–6.9		5.5–5.9	3.5–5.4	3.0–3.4	2.5–2.9		<2.5
Serum creatinine, mg/dL	≥3.5	2.0–3.4	1.5–1.9		0.6–1.4		<0.6		
Hematocrit	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
WBC count, 10^3/mL	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1

GLASGOW COMA SCORE[b,c]			
Eye Opening	**Verbal (Nonintubated)**	**Verbal (Intubated)**	**Motor Activity**
4—Spontaneous	5—Oriented and talks	5—Seems able to talk	6—Verbal command
3—Verbal stimuli	4—Disoriented and talks	3—Questionable ability to talk	5—Localizes to pain
2—Painful stimuli	3—Inappropriate words	1—Generally unresponsive	4—Withdraws to pain
1—No response	2—Incomprehensible sounds		3—Decorticate
	1—No response		2—Decerebrate
			1—No response

POINTS ASSIGNED TO AGE AND CHRONIC DISEASE AS PART OF THE APACHE II SCORE		
Age, Years	**Score**	
<45	0	
45–54	2	
55–64	3	
65–74	5	
≥75	6	

Chronic Health (History of Chronic Conditions)[d]	Score
None	0
If patient is admitted after elective surgery	2
If patient is admitted after emergency surgery or for reason other than after elective surgery	5

Sepsis-related organ failure assessment (SOFA) score.

Organ system	Measure
Respiration	PaO2 to FiO2 ratio
Coagulation	Platelet count
Liver	Serum bilirubin
Cardiovascular	Hypotension
Central nervous system	Glasgow coma score
Renal	Serum creatinine or urine output

Measure	Finding	Points	Day0	Day2
PaO2 to FiO2 ratio	>400 (mmHg)	0		
	300–399 (mmHg)	1		
	200–299 (mmHg)	2		
	100–199 (mmHg)	3		
	<100 (mmHg)	4		
Platelet count	1500/ml	0		
	1000–149 999/ml	1		
	500–99 999/ml	2		
	200–49 999/ml	3		
	<200 per ml	4		
Serum bilirubin	<1.2 mg/dl	0		
	1.2–1.9 mg/dl	1		
	2.0–5.9 mg/dl	2		
	6.0–11.9 mg/dl	3		
	12.0 mg/dl	4		
Hypotension	Mean arterial pressure _ 70 (mmHg)	0		
	Mean arterial pressure <70 then (no pressor agents used) (mmHg)	1		
	Dobutamine any dose	2		
	Dopamine _ 5 mg/kg per min	2		
	Dopamine >5–15 mg/kg per min	3		

	Dopamine >15 mg/kg per min	4
	Adrenaline _ 0.1 mg/kg per min	3
	Adrenaline >0.1 mg/kg per min	4
	Noradrenaline _ 0.1 mg/kg per min	3
	Noradrenaline >0.1 mg/kg per min	4
Glasgow coma score	15	0
	13–14	1
	10–12	2
	6–9	3
	3–5	4
Serum creatinine or urine output		
	Serum creatinine <1.2 mg/dl	0
	Serum creatinine 1.2–1.9 mg/dl	1
	Serum creatinine 2.0–3.4 mg/dl	2
	Serum creatinine 3.5–4.9 mg/dl	3
	Urine output 200–499 ml/day	3
	Serum creatinine >5.0 mg/dl	4
	Urine output <200 ml/day	4

PaO2 is in mmHg and FiO2 in per cent, from 0.21 to 1.00.
Adrenergic agents as administered for at least 1 hour with doses in mg/kg per min.
A score of 0 indicates normal and a score of 4 indicates most abnormal.
Data can be collected and the score calculated daily during the course of the admission.
Interpretation: minimum total score: 0; maximum total score: 24.
The higher the organ score, the greater the organ dysfunction.
The higher the total score, the greater the multiorgan dysfunction.

Mortality rate by SOFA score.

Organ system	0	1	2	3	4
Respiratory	20%	27%	32%	46%	64%
Cardiovascular	22%	32%	55%	55%	55%
Coagulation	35%	35%	35%	64%	64%
CNS	32%	34%	50%	53%	56%
Renal	25%	40%	46%	56%	64%

MASTER CHART

Sl.no	Name	Age	SEX	CRP (mg/dl)	LDH (IU/L)	ESR (mm/hr)	Plt count/mcl	PT (seconds)	Apache 24hrs	AP 48-72
1	Pakkiri	55	M	10.2	522	28	80,000	14	9	6
2	Paleesan	42	M	25.8	340	5	1,56,000	12	7	6
3	Karthick	21	M	1.1	240	120	1,14,000	42	18	*
4	Rajasekar	65	M	17.16	420	36	2,18,000	20	11	14
5	Kumaresan	26	M	7.9	1110	27	68,000	15	3	2
6	Saroja	35	F	11.92	320	40	70,000	23	9	7
7	Mohammed Basha	40	M	29.58	450	36	1,96,000	20	15	7
8	Rajasekar	30	M	11	393	26	2,32,000	13	6	2
9	Niranjan	28	M	18.5	196	42	1,72,000	15	16	9
10	Palani	34	M	38.6	1420	50	1,40,000	18	26	23
11	egavalli	27	F	18.78	1418	31	1,60,000	14	16	*
12	Kumar	36	M	36.58	2540	40	1,20,000	13	24	*
13	Kavitha	29	F	8.7	430	20	1,90,000	26	5	5
14	suresh	28	M	45.3	2344	45	2,56,000	16	14	17
15	Kamatchi	45	F	14	650	25	1,80,000	16	8	5
16	Kuppammal	30	F	24	1200	40	1,67,000	19	14	10
17	subramani	53	M	37	2100	26	1,10,000	23	18	20
18	Mary	58	F	24.6	480	45	2,10,000	19	10	6
19	Saroja	63	F	14.3	690	30	1,30,000	15	8	5
20	kamala	26	F	18.2	550	22	87,000	21	8	6
21	Raji	46	F	23.12	1800	40	1,45,000	26	16	18
22	mani	63	M	7.9	460	24	1,90,000	17	8	6
23	Ponnammal	60	F	22.8	1690	45	1,70,000	22	21	*
24	Elumalai	24	M	12	870	23	1,45,000	14	6	8
25	Perumal	65	M	30.5	1200	20	3,09,000	20	18	17

MASTER CHART –Contd. 2 ,

Sl.no	Name	Sofa 24	Sofa 48-72	Smoking	Alcohol	Hypertension	Diabetes	Diagnosis	Outcome
1	Pakkiri	5	4	Y	Y	N	N	Rt LL pneumonia	Survival
2	Paleesan	0	1	N	N	N	N	UTI	Survival
3	Karthick	12	*	N	N	N	N	ALF	Expired
4	Rajasekar	3	2	N	Y	N	N	Rt UL pneumonia	Survival
5	Kumaresan	3	0	Y	N	N	N	Pneumonia	Survival
6	Saroja	2	2	N	N	N	N	UTI	Survival
7	Mohammed Basha	6	3	Y	Y	N	N	Rt ML pneumonia	Survival
8	Rajasekar	2	1	Y	Y	N	N	Lt LL pneumonia	Survival
9	Niranjan	7	5	N	N	N	N	B/L Bronchopneumonia	Survival
10	Palani	14	14	Y	Y	N	N	Lt LL pneumonia	Expired
11	egavalli	10	*	N	N	N	N	B/L Bronchopneumonia	Expired
12	Kumar	15	*	Y	Y	N	N	ARDS	Expired
13	Kavitha	3	2	N	N	N	N	B/L Bronchopneumonia	Survival
14	suresh	6	7	N	N	N	N	Lepto/ ARDS	Expired
15	Kamatchi	2	1	N	N	N	Y	UTI	Survival
16	Kuppammal	6	4	N	N	N	N	Rt LL pneumonia	Survival
17	subramani	9	12	N	N	Y	Y	Rt LL pneumonia	Expired
18	Mary	4	4	N	N	N	Y	Rt LL cellulitis	Survival
19	Saroja	4	3	N	N	N	N	Lt UL pnemonia	Survival
20	kamala	5	5	N	N	N	N	UTI	Survival
21	Raji	7	9	N	N	N	Y	B/L Bronchopneumonia	Survival
22	mani	2	1	N	N	N	N	Lt LL pneumonia	Survival
23	Ponnammal	13	*	N	N	N	Y	B/L pneumonia	Expired
24	Elumalai	3	3	N	N	N	N	UTI	Survival
25	Perumal	7	9	N	N	N	Y	Rt renal abscess	Expired

MASTER CHART –Contd. 3 ,

Sl.no	Name	Age	SEX	CRP (mg/dl)	LDH (IU/L)	ESR (mm/hr)	Plt count/mcl	PT (seconds)	Apache 24hrs	AP 48-72
26	Venda	43	F	12.8	250	20	2,30,000	16	10	8
27	Chinnaiya	45	M	16	620	18	1,80,000	19	12	7
28	Siva	34	M	6	300	12	70,000	16	6	6
29	Mathialagan	63	M	18	1590	40	1,90,000	28	16	18
30	Ganapathy	38	M	12	457	16	2,87,000	19	6	6
31	Selvaraj	62	M	14	870	20	1,85,000	14	12	15
32	Kalyani	67	F	23	1200	26	2,20,000	22	18	20
33	Maheshwari	56	F	8.3	680	30	1,30,000	14	6	7
34	Angel	35	F	7.12	430	16	1,98,000	16	8	8
35	Kumari	48	F	12.9	980	23	3,45,000	26	14	12
36	Mahesh	25	M	11.8	1100	24	2,10,000	20	14	9
37	Kanagammal	45	F	17	1200	26	2,15,000	20	16	18
38	Sundaram	65	M	13.7	650	20	2,30,000	23	16	16
39	Francis	43	M	15	450	15	3,68,000	12	17	13
40	Kamal	24	M	14	1400	36	1,45,000	15	14	16
41	Kodandam	56	M	24	2100	40	56,000	24	18	22
42	Kamala	38	F	14.26	710	22	80,000	14	12	10
43	Sugumari	72	F	9.7	328	29	68,000	32	12	10
44	Veerammal	38	F	11.7	850	23	3,90,000	16	10	9
45	Sahul	42	M	12.8	920	18	2,30,000	21	13	12
46	James	45	M	7.45	1200	26	4,80,000	14	9	9
47	subbammal	57	F	25.1	1650	24	1,10,000	17	16	18
48	Sivagami	24	F	12	870	42	2,00,000	22	10	7
49	Malliga	44	F	6.9	530	20	3,12,000	18	8	6
50	Rajeshwari	38	F	12	1100	45	2,38,000	26	8	9

MASTER CHART –Contd. 4 ,

Sl.no	Name	Sofa 24	Sofa 48-72	Smoking	Alcohol	Hypertension	Diabetes	Diagnosis	Outcome
26	Venda	4	2	N	N	N	N	Rt LL pneumonia	Survival
27	Chinnaiya	7	6	N	N	N	N	UTI	Survival
28	Siva	3	2	N	Y	N	N	Rt UL pneumonia	Survival
29	Mathialagan	8	8	Y	Y	N	Y	B/L pneumonia	Expired
30	Ganapathy	1	2	Y	N	N	N	Lt LL pneumonia	Survival
31	Selvaraj	6	3	N	N	N	Y	Lt UL pnemonia	Survival
32	Kalyani	10	11	N	N	Y	Y	Rt Psoas abscess	Expired
33	Maheshwari	3	4	N	N	N	Y	UTI	Survival
34	Angel	3	2	N	N	N	N	Rt LL pneumonia	Survival
35	Kumari	8	6	N	N	N	Y	Rt LL cellulitis	Survival
36	Mahesh	6	5	N	N	N	N	Rt LL pneumonia	Survival
37	Kanagammal	11	12	N	N	Y	Y	Rt LL pneumonia	Expired
38	Sundaram	9	7	N	N	N	Y	Rt UL pneumonia	Survival
39	Francis	5	2	N	N	N	N	Rt UL pneumonia	Survival
40	Kamal	10	8	N	N	N	N	Sepsis/ ARDS	Survival
41	Kodandam	8	9	Y	N	N	Y	B/L pneumonia	Expired
42	Kamala	3	4	N	N	N	N	Rt ML pneumonia	Survival
43	Sugumari	6	4	N	N	N	Y	Rt pyelonephritis	Survival
44	Veerammal	6	6	N	N	N	N	UTI	Survival
45	Sahul	8	6	N	N	N	N	Lt UL pnemonia	Survival
46	James	3	4	N	N	N	Y	Rt Psoas abscess	Survival
47	subbammal	7	9	N	N	N	Y	Rt LL pneumonia	Expired
48	Sivagami	4	4	N	N	N	N	Rt LL pneumonia	Survival
49	Malliga	4	5	N	N	N	N	UTI	Survival
50	Rajeshwari	5	5	N	N	N	N	Lt UL pnemonia	Survival

INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To

Dr. Anand .M
PG in Md Internal Medicine
Madras Medical College, Chennai -3

Dear Dr. Anand .M

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled "Serum lactate dehydrogenase and C reactive protein levels in sepsis and its correlation with APACHE-II score" No. 01062011.

The following members of Ethics Committee were present in the meeting held on 24.06.2011 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan, MD	-- Chairperson
2.	Prof. V. Kanagasabai MD Dean, Madras Medical College, Chennai-3,	-- Deputy chairman
3.	Prof. A. Sundaram, MD Vice Principal , Madras Medical College, Chennai -3	-- Member Secretary
4.	Prof R. Sathianathan MD	-- Member
5.	Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	-- Member
6.	Prof. Geetha Subramanian MD DM Prof & Head , Dept. of Cardiology, MMC, Ch-3	-- Member
7.	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	-- Member
8.	Prof. C. Rajendiran .MD Director , Institute of Internal Medicine, MMC, Ch-3	-- Member
9.	Thiru. A. Ulaganathan Administrative Officer, MMC, Chennai -3	-- Layperson
10.	Thiru. S. Govindasamy . BA.BL	-- Lawyer
11.	Tmt. Arnold Soulina	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee